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A.M.A. ARCHIVES OF SURGERY

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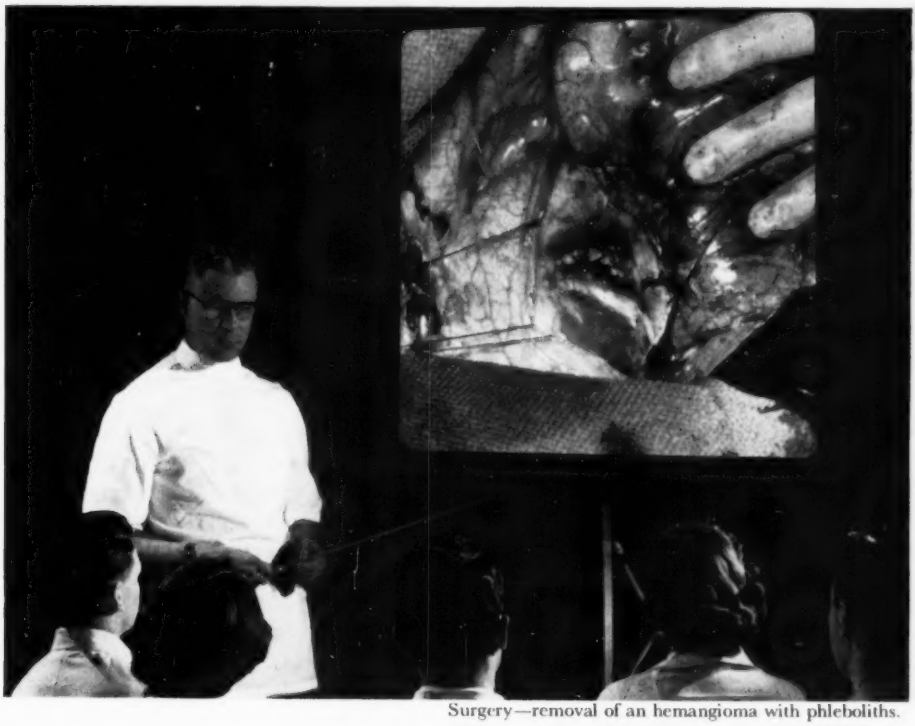

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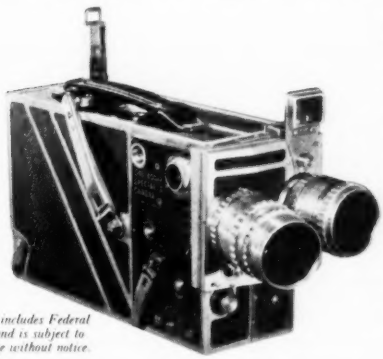

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A.M.A. ARCHIVES OF
SURGERY

Analysis of Forty-Two Shunt Procedures for Portal Hypertension

CORNELIUS E. SEDGWICK, M.D., Boston, and H. ALAN HUME, M.D., Philadelphia

At the present time there is a considerable body of evidence in the surgical literature to support the contention that venous shunting procedures constitute an effective method of controlling hemorrhage from varices of the upper gastrointestinal tract. We are in accord with those authors [1,2,4-6,9] who find these operations useful in the management of selected patients with bleeding esophageal varices, and we wish to present an analysis of 42 operative cases from the Lahey Clinic through 1957 to support this point of view.

In 28 patients splenectomy and splenorenal anastomosis were carried out. In one early case nephrectomy was necessary to effect an anastomosis. As experience with this procedure increases, however, it should rarely, if ever, be necessary to sacrifice a kidney. The eventual mortality (operative and late follow-up) in this group has been 47%.

End-to-side portacaval shunts have been carried out in 13 cases, with a final mortality to date of 46%. One makeshift shunt between the inferior mesenteric vein and the left renal vein was performed. This patient is alive, but clinical evidence suggests that the shunt is not functioning.

In the splenorenal group, there were three operative deaths and one late death from liver failure (14.3%). In the portacaval group, one operative death and two late deaths from liver failure occurred (23%).

No operative deaths were caused by varical hemorrhage in the splenorenal group, but five patients bled to death subsequently. One operative death resulted from bleeding varices which precipitated liver failure in a patient with a portacaval shunt, but no late deaths were caused by bleeding in this group.

The morbidity rate was 76% in the splenorenal group and 50% in the portacaval group. The mortality statistics are summarized for these groups in Tables 1, 2, and 3.

Two factors are of primary importance in the subsequent clinical course of these patients. The first is the anatomic and physiologic status of the liver (Table 4), and the second is the technical adequacy of the shunt.

TABLE 1.—*Types of Venous Shunt Procedures in Forty-Two Patients with Portal Hypertension*

Type of Operation	No. of Patients	Deaths			
		Operative, No.	Late, No.	Total No.	Total Per Cent
Splenorenal	28	3	1	4	14.3
Portacaval	13	1	2	3	23.1
Inferior mesenteric-left renal	1	..	..	0	..
Total	42	4	3	7	16.7

Submitted for publication Sept. 25, 1958.

Department of Surgery, Lahey Clinic (Dr. Sedgwick). Former Fellow in Surgery, Lahey Clinic; trainee, National Cancer Institute, Bethesda, Md. (Dr. Hume).

TABLE 2.—*Operative Deaths Following Shunt Procedures*

Cause of Death	No. of Patients	Type of Shunt	
		Splenorenal	Portacaval
Liver failure	4	3	1
Massive variceal hemorrhage	1	0	1
Tension pneumothorax	1	0	1
Myocardial infarct	1	1	0

It will be noted that we have a higher proportion of patients with biliary cirrhosis (21.4%) than other reported series. This is a consequence of the large number of bile-duct strictures which have been repaired at the Lahey Clinic over the years. This aspect of the problem of portal hypertension is discussed in another communication.[7]

There is a distinct relationship between the adequacy of the shunt and subsequent variceal hemorrhage. Table 5 gives data regarding the postoperative occurrence of esophageal bleeding. Variceal bleeding occurred in 12 of 42 patients (29%), with 6 deaths from bleeding (14%). We are convinced that postoperative variceal bleeding will seldom occur when the shunt is technically adequate (provided subphrenic abscess does not develop)[7] and when the patients are maintained on a reasonable liver regimen subsequently.

Data regarding the 12 patients who bled after shunt procedures are presented in Table 6. It will be seen that the shunt was technically unsatisfactory in all except Cases 5, 6, 7, and 9. Case 5 was a 30-year-old woman with a three-year history of jaundice caused by bile-duct stricture. External drainage of the bile ducts followed by definitive repair was carried out after the initial splenorenal anastomosis for hemorrhaging esophageal varices. At the time of definitive bile-duct repair, a liver biopsy confirmed the gross impression of primary carcinoma. We do not know whether or not this was related to her death from hemorrhage, eight months after splenorenal shunt.

Case 6 was an alcoholic who was unable to abstain. Liver function had deteriorated at a 4-month check-up, and he died 10 months after operation, during an alcoholic debauch.

TABLE 3.—*Late Deaths Following Shunt Procedures*

	Portal Cirrhosis		Biliary Cirrhosis		
	Splenorenal	Portacaval	Splenorenal	Portacaval	Total
Liver failure	1	2			3
Hemorrhage from varices	3		1		4
Myocardial infarct			1		1
Bleeding ulcer (autopsy)				1	1
Multiple myeloma	1				1
Duodenal fistula (later bile-duct surgery)			1		1
Acute glomerulonephritis			1		1
Operative deaths	3	3	1		7

TABLE 4.—*Pathologic Diagnosis at Operation in Forty-Two Cases of Portal Hypertension*

Diagnosis	No. Cases	Operative and Late Deaths	
		No.	Per Cent
Portal cirrhosis	31		
Laennec	24	9	38
Postnecrotic	4	3	75
Unclassified	3	1	33
Biliary cirrhosis	9	6	67
Normal liver	2	0	
Total	42	19	45

TABLE 5.—*Summary of Esophageal Bleeding After Shunt Operations*

Type of Shunt	No. of Patients	Occurrence of Bleeding	Deaths from Bleeding
Normal liver (Extrahepatic block)			
Splenorenal	1	0	0
Portacaval			
Makeshift	1	1	0
Portal cirrhosis			
Splenorenal	19	4	2
Portacaval	12	3	1 *
Biliary cirrhosis			
Splenorenal	18	4	3
Portacaval	1	0	
Total	42	12 (29%)	6 (14%)

* Operative death.

TABLE 6.—*Correlation of Bleeding After Shunt Procedures with Operative Appraisal of Anastomosis*

Case	Type of Shunt	Operative Appraisal	Dead of Bleeding	Comment
1	Splenorenal	Inadequate—tear in splenic vein repaired	—	Bled 3 yr. after shunt; still alive
2	Portacaval	Unsatisfactory—thrombus in wall of portal vein	—	Splenectomy elsewhere 2 yr. after portacava shunt
3	Inferior mesenteric-left renal	Inadequate—small vessels	—	Extrahepatic block; previous splenectomy
4	Splenorenal	Unsatisfactory—very small vein; age 12 yr.	+	Active ulcerative colitis
5	Splenorenal	Good shunt	+	Primary carcinoma found in liver biopsy; benign bile-duct stricture
6	Splenorenal	Adequate shunt	+	Died during alcoholic spree
7	Portacaval	Excellent shunt	+	Died 5th postoperative day; at necropsy shunt was widely patent; stomach contained 500 cc. of blood from distal esophagus
8	Portacaval	Unsatisfactory—thrombus in wall of portal vein	—	Healed duodenal ulcer at time of shunt; varices smaller as seen by postoperative X-ray
9	Splenorenal	Adequate shunt	—	Alive 1 yr. after shunt; 1 hemorrhage; large gastric varices demonstrated by x-ray
10	Splenorenal	Inadequate—tear in renal vein	+	Bled 2 wk. after operation; died of second hemorrhage 11 mo. after operation
11	Splenorenal	Inadequate—small splenic vein	+	Evisceration, omental hemorrhage, and liver failure after operation
12	Splenorenal	Questionably adequate—small splenic vein	—	Bled 3 wk. after operation; pleural effusion and possible subphrenic abscess; alive after 6 mo.

Case 7 was a 25-year-old woman who had contracted infectious hepatitis during a pregnancy the previous year. She had intractable ascites and required 44 paracenteses for removal of fluid before the time she came to the clinic. While she was in the hospital for study, a massive hemorrhage occurred. Four days later a portacaval shunt was performed. She did well for four days and went into shock on the fifth postoperative day. The clinical impression was pulmonary embolism. At necropsy, the portacaval shunt was widely patent, with no evidence of leakage or undue reaction about the anastomosis and no thrombus in either the caval or the portal venous system. The stomach contained 500 cc. of blood, which apparently had come from the distal portion of the esophagus, although no evidence of ulceration over a varix in this area was noted. In retrospect, we would prefer to have treated this patient with tamponade compression of the esophagus and carry out a portacaval shunt under more favorable circumstances.

Shunt procedures should not be performed on an emergency basis; in a small group of patients, however, the problem of active, uncontrollable hemorrhage arises. The operative choice is portacaval or splenorenal shunt with tamponade in place, transesophageal suture ligation of the varices, or limited esophagogastric resection. The mortality and morbidity associated with the last procedure in the presence of active bleeding is prohibitive. We have had one other case in which tamponade compression would not control the bleeding once the bag was decompressed. A portacaval shunt was carried out successfully with the tamponade in place.

Case 9 was a 36-year-old woman who had undergone six operations on the biliary tract prior to the splenorenal shunt procedure. One episode of hematemesis and melena occurred eight months after operation. Roentgenologic examination at that time showed a lesion in the proximal portion of the stomach, which probably represents large gastric varices.

That protection from bleeding is not absolute is a clinically accepted fact. Bleeding from varices may occur despite the presence of an adequate shunt.[3] Adequate biliary

TABLE 7.—*Status of Varices After Shunt Procedure*

Status	Splenorenal	Portacaval	Makeshift
Smaller	9	3	
Unchanged	2	0	
Larger	0	1	
No data	17	9	1
Total	28	13	1

TABLE 8.—*Liver Function After Shunt Procedure*

Studies	Total Cases	Per Cent		
		Improved	Same	Worse
Albumin	28	25	50	25
Cephalin flocculation	23	35	43	22
Bilirubin	21	43	24	33
Sulfobromophthalein (Bromsulphalein)	19	31	17	52

decompression has persisted in Case 9, and we contemplate no further surgical treatment unless hemorrhage recurs.[7]

Results of esophagograms in 15 patients substantiate the reports of other authors regarding the postoperative size of varices (Table 7).

One instance of size increase of esophageal varices (Table 6, Case 2) was noted 20 months after portacaval shunt. This patient was operated on elsewhere 26 months after portacaval shunt for massive hemorrhage from the upper gastrointestinal tract. Splenectomy and ligation of the coronary veins were performed, and the surgeon noted that the previous portacaval shunt was thrombosed. The patient had refused our suggestion of splenorenal shunt when we noted a significant increase in the size of the varices 20 months after the portacaval shunt.

The results of our follow-up studies of liver function are quite similar to those reported by Ellis, Linton, and Jones.[4] We have used their criteria for significant change in liver function and have tabulated these figures, as well as material in several of the other tables in similar fashion to facilitate comparison of the two series (Table 8). The greater improvement in bilirubin levels in our series reflects the higher percentage of cases of biliary cirrhosis secondary to bile-duct obstruction and a more complete follow-up on this particular group of patients.

Precise comparison of liver function among patients is impossible, as this factor is so readily influenced by the degree of patient cooperation in long-term liver therapy and the duration of time between surgery and study of liver function in relationship to this cooperation. For consistency in comparison, we have used data from the last follow-up study.

One patient with a portacaval shunt died from the physiologic consequences of unrecognized tension pneumothorax. Excluding this case from the series gives us a similar mortality rate in the splenorenal and portacaval groups. The morbidity rate is significantly higher in patients subjected to splenorenal shunt. This, again, may be related to the larger proportion of patients with severe biliary cirrhosis and active hepatitis who have suffered one or more massive hemorrhages.

Postoperative neurologic symptoms have occurred in only one case in the entire series. They followed splenorenal shunt in a patient with biliary cirrhosis. Delayed neurologic signs appeared in one patient with a portacaval shunt, but were readily controlled by reducing the protein intake. Since we have no autopsy proof of the patency of splenorenal shunts in a large series of patients without neurologic signs, we are inclined to feel that the lower incidence of neurologic sequelae in this group may be related to prompt thrombosis of the splenorenal shunt.

Until the relationship of complete diversion of portal blood from a liver which is the seat of an active pathologic process to further loss of liver function is settled, we shall continue to carry out splenorenal shunts in some cases in which portacaval shunt would probably afford greater protection from hemorrhage.

Some authors [5] have stated that the addition of a venous shunt procedure to splenectomy does not increase the operative

risk when the liver is normal. We do not have sufficient clinical evidence to dispute this point, but a previous communication [8] has shown that in the presence of even slight liver dysfunction the mortality associated with such a procedure is significantly increased and the morbidity increased threefold.

Summary

We report the results of clinical and laboratory follow-up studies in a series of 42 patients in whom direct venous shunts have been carried out for portal hypertension. The follow-up period varied from one to eight years.

The over-all late mortality was 45% and the operative mortality rate 16.6%. We noted a decrease in size of varices postoperatively in 12 of 15 patients whose preoperative and postoperative roentgenograms were available for comparison.

Factors related to failure of these procedures to afford even greater protection from hemorrhage include technical adequacy of the shunt, the anatomic and physiologic status of the liver, and the subsequent development of a complication such as subphrenic abscess. There is little doubt that many of the operative survivors will live for many years.

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A Clinical and Pathologic Analysis of Rupture of Aortic Homografts

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Introduction

The need for a method of bridging defects in major arteries in various injuries and diseases has long been felt. The attempts to restore vascular continuity have led to the use of various substances. Carrell, in 1910, was the first to investigate the functional and histological results with preserved arterial homografts.[1] He used as grafts the carotid arteries of dogs. These vessel segments were kept in a refrigerator in different media for varying periods of time. The media used were isotonic saline, Locke's solution, humid air, and defibrinated blood.

Gross[2] reintroduced the arterial graft, and since 1948 the problem has been vigorously studied. It is now generally believed that several methods of storage and preservation of vascular grafts are acceptable. These include the following:

1. Storage in nutrient media at 1-4 C[2]
2. Deep-freeze techniques[3,4]
3. Lyophilization[5-8]

In addition to the problems of storage, the need for sterilization of the vessel segments has arisen. Techniques in use are (1) formalinization, (2) irradiation,[9,10] (3) ethylene oxide,[11,12] and (4) β-propiolactone.[13]

It is felt that these methods of preservation and storage of vessel segments give reliable homografts which are sterile and will not disrupt.[10] However, fatal ruptures of aortic homografts have occurred and have been reported.[14-18] Barnes and coworkers, in a recent publication,[19] presented 10 deaths due to graft failures in a total series of 165 cases. In four cases graft rupture had occurred. The remaining six cases exhibited fatal hemorrhage at the suture line.

It is our feeling that fatal graft rupture occurs more frequently than has been reported to date. It is the purpose of this article to present a clinical and pathologic analysis of three cases of aortic homografts prepared by presently accepted methods of processing which resulted in fatal disruption when used clinically.

Graft Data

All grafts used were obtained from the Blood Vessel Bank of the Cornell Medical Center at New York. The method of processing of three grafts consisted of sterilization, followed by lyophilization and subsequent storage at room temperature in sealed vacuum glass tubes. The remaining graft was prepared by the deep-freeze technique and kept frozen until use. Sterilization was performed in all cases with ethylene oxide.

Table 1 contains the data on the collection and preparation of the homografts.

Presentation of Cases

CASE 1.—*Clinical History.*—A 46-year-old white man was admitted to Mount Sinai Hospital for the first time, with a history of development of claudication of the lower extremities six years prior to this admission. Three years later the patient had developed persistent hypertension. He was admitted because of severe headaches.

On admission, the blood pressure was 240/120; severe retinopathy was present, and there were no

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TABLE 1.—*Data on Collection and Preparation of Homografts*

Case No.	Age of Donor	Time of Collection, Hours Post Mortem	Date Sent to Bank	Date & Method of Sterilization	Date & Method of Preservation
1	40	25	9/15/56	10/3/56 Ethylene oxide	9/15/56 Deep-freeze
2	57	15	8/2/57	8/8/57 Ethylene oxide	8/8/57 Lyophilization
3	51	4	8/8/57	8/13/57 Ethylene oxide	8/13/57 Lyophilization
4 *	43	20	7/24/57	7/25/57 Ethylene oxide	7/25/57 Lyophilization

* Patient died 163 days after successful repair of abdominal aortic aneurysm ;graft intact. Presented for comparison.[10]

palpable pulses in the lower extremities. An aortogram revealed complete occlusion of the abdominal aorta below the level of the right renal artery and involving the left renal artery.

On Oct. 4, 1956, the patient underwent an aortic intimectomy at the level of the right renal artery, and an aortic resection and placement of an aortic bifurcation homograft. The postoperative course was benign until the morning of the fifth postoperative day, when the patient suddenly went into shock and died.

Postmortem Findings.—Gross: The abdominal cavity contained 2,000 cc. of freshly clotted and liquid blood. Just below the level of the right renal artery there was a suture line joining the host aorta and the homograft. Blood could be expressed by gentle pressure from a pinpoint-like lesion on the left anterior aspect of the graft. This was located immediately below a point of passage of a suture of the proximal anastomosis.

The right leg of the graft was sutured to the right external iliac artery, and the left leg of the graft was sutured to the left femoral artery. The right femoral artery was occluded by an organizing thrombus 5 cc. below the right-sided anastomosis. A fresh thrombus was propagated in a retrograde fashion and extended into the lumen of the graft (Fig. 1). No other significant defects of the graft or host aorta were demonstrable.

Microscopic: Examination of the proximal anastomosis showed an intense inflammatory reaction to be present in the adventitia of the homograft. This was limited, however, to the region of the disruption of the graft in the vicinity of the suture material (Fig. 2*A*, *B*). In this region the elastic fibers of the media were disrupted (Fig. 2*C*). Other areas of the homograft exhibited well-preserved, nonfragmented elastic fibers in the media.

The remainder of the graft exhibited a narrow band of pseudointima, a relatively acellular media, and mild adventitial reaction.

The distal anastomoses were found to be free of any significant inflammatory reaction.

CASE 2.—*Clinical History.*—A 63-year-old white man was admitted to Mount Sinai Hospital because of an enlarging abdominal mass of three months' duration.

On admission the blood pressure was 120/70 and the pulse 60 a minute and regular. There was no evidence of cardiac or renal disease on work-up. An x-ray of the abdomen revealed aneurysmal dilatation and calcification of the abdominal aorta.

On Oct. 4, 1957, a fusiform aneurysm of the abdominal aorta was removed and replaced by a

Fig. 1.—Intimal surface of aortic homograft, dissected in situ and opened posteriorly. The medial arrow points to the area of hemorrhage beneath the proximal anastomosis. The lateral arrow points to the ligated left renal artery. A thrombus is seen in the right femoral artery.

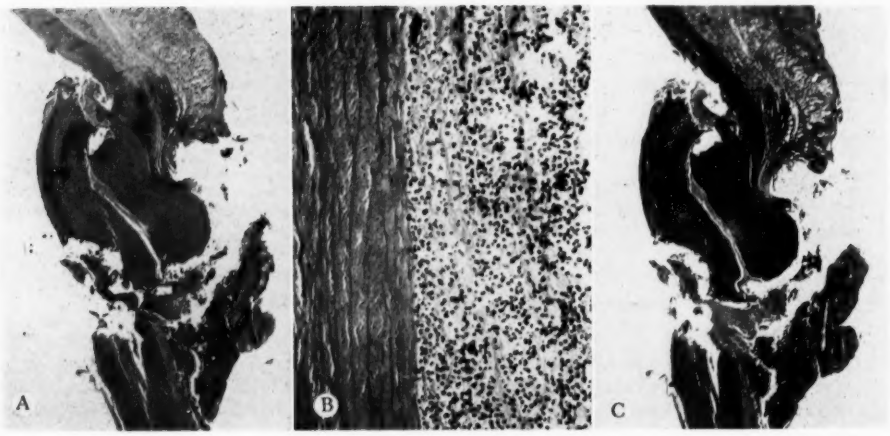


Fig. 2.—*A*, photomicrograph of proximal anastomosis between host aorta (upper portion of picture) and homograft (lower portion of picture). Suture material and an inflammatory reaction in the adventitia are seen in the area of perforation. Hematoxylin-eosin stain; reduced to 60% of mag. × 20.

B, photomicrograph of inflammatory process in the adventitia of the graft. Hematoxylin-eosin stain; reduced to 60% of mag. × 196.

C, photomicrograph of proximal anastomosis, as in *A*. Note the disruption of the elastic fibers of the media at the site of perforation. Weigert-Van Gieson stain; reduced to 60% of mag. × 20.

homograft. The aneurysm was located below the renal vessels and did not involve the aortic bifurcation.

The postoperative course was uneventful until Oct. 10, when the patient complained of pain in the abdomen and back. On Oct. 13 (ninth postoperative day) the patient had a sudden drop in blood pressure and died shortly thereafter.

Postmortem Findings.—Gross: The retroperitoneal space contained 700-1,000 cc. of semiclotted and fresh blood. Examination of the homograft revealed both the proximal and the distal anastomotic suture line to be intact, with no evidence of leakage or disruption (Fig. 3*A*). On opening the aorta, a 1.5×0.5 cm., irregular-shaped ulceration was noted on the posterior wall in the midportion of the homograft. It was surrounded by a slightly raised and wrinkled intimal surface (Fig. 3*B*).

The external surface of the defect was covered by a thin membrane of dark clotted blood. Four openings in the posterior wall of the graft, representing lumbar arterial branches, were probed and

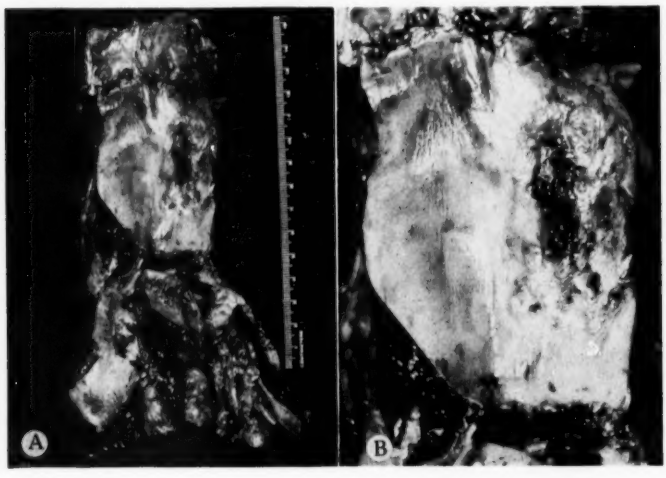


Fig. 3.—*A*, intimal surface of aortic homograft which ruptured on the ninth postoperative day. Note site of rupture, as well as intact anastomotic suture lines.

B, close-up view of *A*, showing area of intimal ulceration and perforation.

Fig. 4. — Photomicrograph of a section taken near the area of perforation seen in Figure *3B*. Branching septate hyphae of fungus can be seen in the intimal layer of the homograft. Hematoxylin-eosin stain; reduced to 92% of mag. × 59.

found to be well ligated. Two other lumbar arterial openings were found in the region of the ulcerated defect. One was found to be patent, and the ligature was easily removed from the area.

The arch and the thoracic and descending abdominal aorta revealed moderate atherosclerotic changes.

No other cause of the retroperitoneal hemorrhage was found.

Microscopic: Histological sections were prepared from the regions of the proximal and distal anastomoses. Also, multiple sections were taken proximal to, through, and distal to the area of defect.

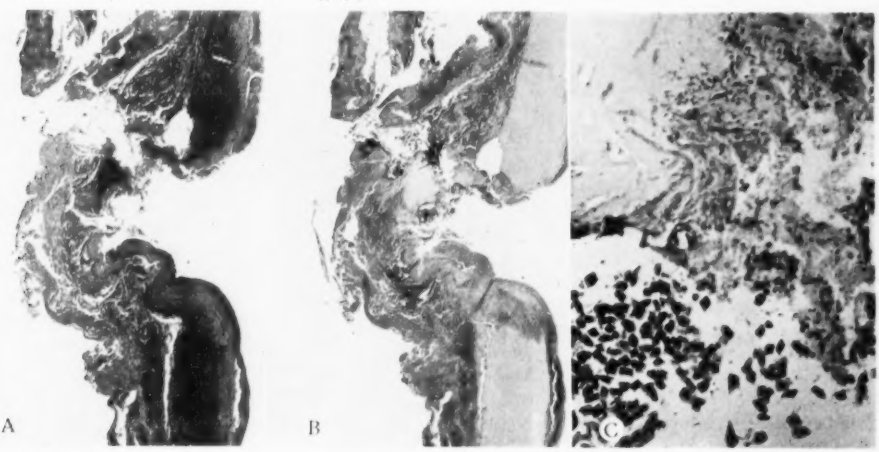
The proximal anastomosis exhibited slight necrosis of the intimal surface with moderate polymorphonuclear- and round-cell infiltration. The elastic fibers of the media were well preserved, with no areas of disruption. The distal anastomosis was free of any inflammatory reaction and exhibited a thin pseudointima and an acellular media.

Sections through and immediately adjacent to the area of graft rupture revealed the presence of a fungus (Aspergillus) in the intima. There was a surrounding cellular reaction, consisting of polymorphonuclear and round cells. No fungus or cellular infiltration was found in the media or adventitia

Fig. 5.—*A*, photomicrograph of a section through the site of rupture seen in Figure *3B*. Complete disruption of the elastic fibers of the media is seen at one point. Weigert-Van Gieson stain; reduced to 61% of mag. × 20.

B, photomicrograph of area seen in *A*. Suture material is seen in the region of the homograft rupture. Hematoxylin-eosin stain; reduced to 61% of mag. × 20.

C, photomicrograph of region of suture material seen in *B*. Branching septate hyphae of fungus with surrounding cellular reaction are seen adjacent to the suture material. Hematoxylin-eosin stain; reduced to 61% of mag. × 196.



(Fig. 4). Areas of necrosis were present surrounding the fungus.

The elastic fibers of the media were fragmented, with complete rupture occurring at one point (Fig. 5*A*, *B*). Both suture material and fungus were seen at this area, which corresponds to the region of the ligated lumbar artery branch (Fig. 5*C*). Hemorrhage was also noted to be present in this area.

Fungus was not found in analyzing the other tissues taken post mortem, or in other sections of the graft or host aorta.

CASE 3.—*Clinical History.*—A 58-year-old white man noted a gradually enlarging mass in the lower quadrant of the abdomen. This increase in size occurred over a one-year period, but the mass had become painful in the two weeks prior to admission. There had been 10 previous admissions to the urological service for nephrolithiasis and a total of six ureterolithotomies performed bilaterally.

On admission the blood pressure was 118/70, and the pulse 72 a minute and regular. The physical examination was essentially negative with the exception of a 10-15 cm., tender, pulsatile mass in the left lower quadrant. The femoral artery pulses were palpable.

X-rays revealed the calyces of the left kidney to be dilated and to contain a stag-horn calculus. A work-up for hyperparathyroidism was negative.

On Sept. 20, 1957, a 5×7 cm. aortic aneurysm was resected and a homograft inserted. The aneurysm originated below the renal vessels and involved the bifurcation of the aorta and the common iliac vessels. On July 21 the patient developed anterior chest pain. An EKG was compatible with myocardial damage or pulmonary embolism. Chest x-rays were negative. On Oct. 5 he developed abdominal pain and tenderness of varying degrees of severity, associated with increased bowel sounds. This persisted until Oct. 17 (27th postoperative day), when the patient had a clonic seizure, and vital signs could not be obtained. Immediate bedside laparotomy was performed, in view of the possibility of graft rupture. The posterior peritoneum was bulging, owing to the presence of 2-3 liters of semiclotted and fresh blood. Examination of the graft revealed a perforation to be present in the anterolateral aspect of the midportion of the graft (Fig. 6).

Postmortem Findings.—Gross: There was mild to moderate atherosclerosis of the ascending and upper descending aorta. An anastomosis was present between the aorta and the homograft, 6 cm. below the renal vessels. The graft extended 3 cm. and was transected there. An opened segment of homograft was submitted separately. The distal, transected end of the aorta in the body was just above the bifurcation of the aorta. The bifurcation

Fig. 6.—Intimal surface of aortic homograft which ruptured on the 27th postoperative day. The area of the proximal and distal anastomoses is shown. Note that the suture lines are intact, with no areas of separation. An area of perforation is seen in the proximal portion of the graft.

graft was anastomosed to the respective common iliac vessels (Fig. 6).

All anastomotic suture lines were intact, with no evidence of disruption.

Microscopic: Sections for histological analysis were taken from the anastomotic sites, the region of rupture, and normal-appearing areas of the homograft. The areas of anastomoses revealed little cellular infiltration, with no inflammatory response. The presence of a well-preserved layer of elastica was seen.

Other sections of the graft revealed the same histological pattern with the exception of the area of perforation. In this section there was an inflammatory response in all the layers of the graft wall, with tissue necrosis occurring (Fig. 7*A*).

Fragmentation, separation, and disruption of the elastic fibers of the media were also present in this one region (Fig. 7*B*). No cause for this was observed microscopically. The thoracic portion of the graft used in this case was taken from the vessel bank, removed from its sterile container, and cultured for fungi and bacteria, with no growth resulting.

The clinical events of the three cases presented are summarized in Table 2.

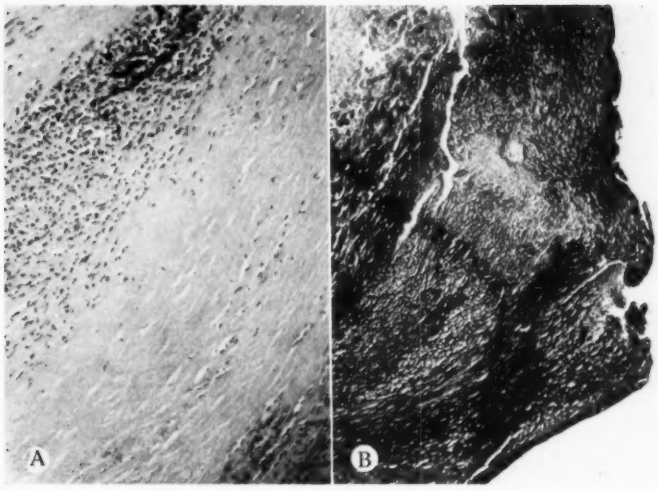


Fig. 7.—*A*, photomicrograph of aortic homograft in region of perforation. There are cellular infiltration of the intima (upper left aspect of photograph), slight cellular infiltration of the media, and marked adventitial reaction (lower right aspect of photograph). Hematoxylin-eosin; reduced to ⅔ of mag. × 59.

B, photomicrograph of aortic homograft in region of perforation, showing fragmentation and disruption of the elastic fibers of the media. Weigert-Van Gieson stain; reduced to ⅔ of mag. × 59.

Comment

The ultimate biologic fate of homografts has been shown to be dependent upon the mechanical integrity of the original components of the vessel wall. Since the connective tissue replacement of adventitia and outer media is slow, inconstant, and incomplete, the performance of the graft depends upon the tissue originally implanted. According to Szilagyi,[17] there is eventual loss of all tissue elements save elastic fibers and a lack of true replacement by the host. The total outlook, then, is one of diminishing strength with increasing age. The anticipation of ultimate dilatation, aneurysm formation, and disruption with long-term follow-up studies[21] presents a real problem in the use of homografts as a suitable replacement for aortic aneurysms.

TABLE 2.—*Summary of Cases*

Case No.	Time of Rupture, Days Postop.	Site of Rupture	Interval Between Onset of Symptoms and Fatal Rupture, Days
1	5	Below proximal suture line	6
2	9	Middle of graft posteriorly	3
3	27	Middle of graft anterolaterally	12

The problem of homograft rupture in the immediate postoperative period appears also to be existent and of grave importance. In these cases the over-all mechanical integrity of the vessel is good. However, one defective area is present and of fatal consequence. Reasons for these disruptions are speculative. Factors incident to the collection and preparation of these vessels may be responsible for their rupture. The elastica in the vessel wall may be stretched while dissecting the vessel at the autopsy table. Inadequate sterilization is suggested by the finding of fungus in Case 2. The presence of the surrounding cellular reaction, as well as the localization of the fungus to the immediate area of homograft rupture only, eliminates the possibility that these organisms were postmortem contaminants. The postulated chain of events would appear to be as follows:

1. Fungus introduced at time of procurement of vessel segment
2. Ineffective sterilization
3. Growth in body following insertion of graft
4. Inflammation and necrosis of homograft wall
5. Weakening at area of ligature of lumbar artery leading to fatal rupture

Weakening of the vessel wall during the lyophilization process, due to formation of ice crystals, may occur[10] and be of significance. Also to be considered is the trauma

to the graft during the rehydration period, as well as potential technical errors associated with ligation of the vessel stumps of the aortic branches. The role of the immune response to a foreign graft as a factor in graft degeneration and failure has also been postulated.[17,22] Whatever the etiology, the cases presented indicate that graft rupture does occur under the existing methods of collection, sterilization, and preservation of arterial homografts.

Analysis of the clinical history of the cases presented shows the necessity of being cognizant of graft rupture and of avoiding fatal delay in treatment. Two of the three cases had premonitory symptoms of severe back and abdominal pain 3 and 12 days, respectively, prior to the fatal disruption.

In addition to the problems of early histological degeneration of the grafts, there is the more serious problem of late degeneration. The early one- or two-year results after homograft placement have been excellent in the majority of cases, but enough disruptions of these grafts have been reported to cause some concern. In addition, animal studies have revealed a high incidence of graft degeneration in three or four years.[23]

Because of our experiences noted above, and those mentioned in the literature, we are now using plastic arterial grafts almost exclusively in our clinic. We find that though, at times, technical difficulties, such as suturing, are greater with these plastic grafts, they are of minor consequence, and the results have been excellent.

Summary and Conclusions

A clinical and histopathologic analysis of three cases of aortic homografts sterilized with ethylene oxide, with fatal postoperative disruption of the grafts, is presented.

An inflammatory response, with tissue necrosis and fragmentation of the elastica, was observed in all the cases to be present only at the site of disruption.

Etiologic factors in postoperative homograft disruption are discussed.

Two of the three cases presented had significant delay between the onset of symptoms postoperatively and the fatal rupture of the graft.

It is suggested that, because of the great possibility of error in the detailed collection and preparation of homografts, the use of suitable plastic arterial grafts be encouraged.

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Aortic-Carotid Bypass Prothesis in Treatment of "Pulseless Disease"

Report of a Case

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Thrombo-obliterative disease of the branches of the aortic arch, also known as "pulseless disease," or Takayasu's disease,[1] is a condition of uncertain etiology, characterized by a lack of pulsation in one or more of the major branches of the aortic arch and ischemic manifestations in the area of distribution of the occluded vessels.

Surgical correction of this condition has been attempted in eight cases. Two were reported by Shimizu and Sano,[2] who attempted thrombectomy through the sacrificed external carotid artery in one case and resected the carotid bifurcation, using a venous homograft between the common and internal carotid arteries in a second case. Thromboendarterectomy was performed in five cases.[3-6] The first instance of surgical correction employing a bypass was reported by De Bakey and co-workers.[4] Treatment was directed toward relief of claudication in the upper extremity, and a nylon bifurcation prosthesis was implanted from the aorta to the subclavian and internal carotid vessels.

We wish to report the following case, the second on record utilizing a bypass graft. Treatment was directed in this instance toward relief of cerebral manifestations, the patient having survived three episodes of transient hemiparesis prior to surgical intervention.

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Report of Case

A 45-year-old white man, a cook, awoke at 6 a. m. on Feb. 21, 1958, with flaccid paralysis of the right side of the body. His speech was slurred and thick. He was examined at that time by his family physician and sent to the hospital. Within two hours there was complete clearing of symptoms. Inquiry revealed that about three months prior to this episode, while watching television, he "felt pins and needles" from his toes up to his head on the right side of the body. Transient right-sided paralysis with associated thick, incoherent speech ensued. This lasted 20 minutes, and recovery was complete. In December, 1957, a similar episode occurred, lasting 30 minutes.

His past history revealed a number of attacks of syncope without detectable cause. Appendectomy and cholecystectomy were done in 1934. In 1943 he was inducted into the Army and served as a baker, only to be discharged in 1945 as "unfit for duty" because of bilateral cryptorchism. He remembered having attacks of vertigo almost weekly while in the Army, but there was no history of any convulsive disorder. He had always been told he had low blood pressure. He smoked two packs of cigarettes daily and had a chronic productive cough. A skull fracture was sustained in an automobile accident in 1951.

Examination revealed a 45-year-old white man in no distress. His appearance was somewhat eunuchoid, with sparse beard and delicate skin. His pupils were equal and reacted well to light and in accommodation. The ocular fundi were not remarkable on routine inspection. The intraocular pressure was 16 mm. Hg. Under ophthalmoscopic observation, slight digital pressure on the left globe resulted in obliteration of the central retinal artery and blanching of the optic disc, with associated loss of light perception. This sign was considered indicative of a definitely subnormal central retinal artery pressure. Pressure on the right globe also resulted in obliteration of the artery, pallor of the disc, and loss of light perception. However, considerably more pressure was required to produce this effect on the right side.

No auscultatory blood pressure was obtainable in either arm. No pulses were palpable in either upper extremity. No subclavian pulsations were present. The right carotid pulse was felt, and a thrill was evident when this vessel was palpated. A definite murmur could be heard over the carotid bulb. Neither temporal pulse was present. The left carotid pulse was absent. Femoral, dorsalis pedis, and posterior tibial pulsations were present bilaterally.

The heart was normal in size and shape. No murmurs were heard. The lungs were clear. No abdominal organs or masses were felt. The testes were not palpable, and the external genitalia were small. Rectal examination was negative. There were no residual neurological abnormalities at the time of examination. Muscle strength was normal. Knee and ankle jerks were normal. No Babinski sign was present. A spinal puncture on admission revealed 3 lymphocytes per cubic millimeter, 35 mg. % of protein, and 62 Somogyi units of sugar. Serologic tests for syphilis were negative. The hematocrit was 48%; the hemoglobin 96% (15 gm. %). The white blood cell count was 10,250, with a normal differential count. The NPN was 39 mg. %, and total cholesterol 304 mg. %. Platelets totaled 187,000 per cubic millimeter.

The electrocardiogram was normal. The electroencephalogram showed no abnormal changes, even on hyperventilation. Chest and skull x-rays were normal. Oscillometric readings were very low in the arms and normal in the legs.

A diagnosis of aortic-arch syndrome with occlusion of the right subclavian, left carotid, and left subclavian arteries was made. On March 5 operation was performed. The left neck was explored through an oblique vertical incision at the anterior border of the left sternocleidomastoid muscle. The carotid sheath was opened; the internal jugular vein was retracted and the carotid artery exposed from the root of the neck upward beyond the bifurcation into the external and internal carotid branches. The artery was shown to be patent in its upper common carotid portion by palpation and aspiration. Accordingly, a left lateral thoracotomy was performed through the bed of the fifth rib, the fourth rib being cracked posteriorly to achieve wider exposure. The mediastinal pleura was opened to expose the arch of the aorta. The left subclavian and common carotid arteries were smaller than normal and were not pulsating. There was some thickening of these vessels and of the immediately adjacent aorta, suggestive of atherosclerosis. Elsewhere the aorta was of normal consistency.

Using a curved De Bakey aortic clamp, the arch of the aorta was grasped tangentially in its descending portion beyond the origin of the left subclavian, to exclude a portion of this vessel from

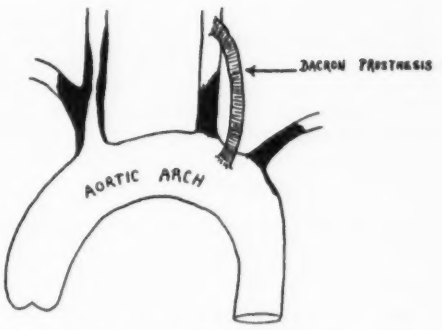

Diagram illustrating location of thrombo-obliterative areas (black) and Dacron prosthesis.

the general circulation. A longitudinal 1 cm. incision was made in the clamped-off portion, and a prosthesis of "microcrimped" Dacron,* measuring 1 cm. in diameter, was anastomosed to the aorta in end-to-side fashion with a running 0000 arterial silk suture, applied in over-and-over fashion and interrupted twice. The Dacron tube was then drawn upward through the dome of the pleura behind the manubrium sterni into the anterior portion of the neck to the upper portion of the left common carotid artery. Here a similar end-to-side anastomosis between graft and carotid was performed. The vascular clamps were released, and good flow and pulsations were established through the graft into the left carotid system. The field was dry at the close of the procedure. Minor oozing through the preclotted prosthesis was easily controlled by sponge pressure for a few minutes. The patient left the operating room in excellent condition, having received 1,000 cc. of blood during surgery.

Following operation the patient experienced difficulty in raising secretions and required repeated tracheal aspirations to clear his upper respiratory passages. Probably related to this difficulty, he developed Staphylococcus pyogenes aureus pneumonia, temperatures ranging from 100 to 102 F and persisting from the 2d through the 15th postoperative day. A good response to novobiocin was ultimately obtained, this antibiotic being suggested by appropriate sensitivity tests. The patient received prophylactic heparin postoperatively, and after 10 days treatment was switched to bishydroxy coumarin U. S. P. (Dicumarol), on which medication he is being maintained.

The graft can be felt pulsating in the neck, and a pulse of good quality is present in the left preauricular region.

On March 27 ophthalmoscopic examination revealed a definite increase in pressure in the central

* Supplied by Ethicon Suture Laboratories, Somerville, N. J.

retinal artery on the left. The lack of a suitable instrument precluded the quantitative estimation of the pressure required to obliterate the retinal arterial pattern. However, the observations recorded were made by the same person both prior to and after surgery.

Comment

There has been much discussion concerning the etiology of thrombo-obliterative disease of the branches of the aortic arch. The following pathologic entities have been suggested: syphilitic aortitis with and without aneurysm; atheromatosis; trauma with and without aneurysm; congenital anomalies; chronic dissection of the aorta; thrombophilia; nonsyphilitic aortitis; embolism; thromboangiitis obliterans, and rheumatic inflammation of the aortic wall. These have been discussed by Ross and McKusick,[3] Kalmansohn and Kalmansohn,[7] and Wagener.[8] The condition is said to be more prevalent in females than in males. In this connection our case is of some interest because of the patient's bilateral cryptorchism and eunuchoid appearance.

The aortic-arch syndrome may give rise to any of the following symptoms:

1. Cerebral: Dizziness, vertigo, aphasia, syncope, headache, convulsions, transient or permanent hemiplegia.

2. Ocular: Transient blindness, cataracts, optic nerve atrophy, and decreased arterial pressure in the retinal vessels. Wagener[8] has made the ocular manifestations of pulseless disease the subject of an extensive review.

3. Upper Extremities: Claudication, weakness, paresthesias, trophic changes, absence of pulsations, and inability to obtain an auscultatory blood pressure.

4. Face: Muscular atrophy, ulceration of palate and nasal septum, and claudication of the muscles of mastication.

The treatment of thrombo-obliterative disease of the aortic arch was unsatisfactory until recently. Advances in surgical techniques now permit rational and effective therapy. It has been pointed out by De Bakey et al.[4] and Ross and McKusick[3] that the severest and irreversible symptoms are in the head. Indeed, cerebral ischemia is the commonest cause of death. One facet of the disease process emphasized by De Bakey et al.[4] deserves repetition, namely, the segmental character of the obliterative arterial process. It is this segmental feature that enables the surgeon to bypass the obstruction.

Surgical restoration of blood flow should be attempted in every case of aortic-arch syndrome where prevention of further damage or amelioration of incapacitating symptoms can be done with a reasonable expectation of success. Our patient suffered three transient hemiplegias, each severer than the preceding, and it was felt that a permanent hemiplegia or fatal cerebral damage would eventually occur. To forestall this, surgical restoration of the blood supply was undertaken. The presence of a murmur and thrill in the patent right common carotid artery made one feel that this vessel, too, was undergoing gradual occlusion. It was hoped that restoration of flow on the left side would temporarily support the patient should the opposite common carotid become occluded. Aortic-carotid bypass will be considered on the right side should the patient be threatened by this eventuality.

Conclusions

A case of aortic-arch syndrome ("pulseless disease") with attacks of transient hemiplegia is described.

The segmental nature of the lesion is again emphasized.

Surgical amelioration of the condition by successful aortic-carotid bypass, utilizing a Dacron prosthesis, is reported.

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Addendum

The patient has been followed for seven months after surgery. There have been no further right-sided cerebral symptoms. The occurrence of transient numbness of the left

arm and side of face on one occasion, in September, 1958, points toward possible progression of disease in the right carotid system, which may necessitate bypass surgery on this side. He is still on bishydroxycoumarin U. S. P. (Dicumarol).

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Prophylactic Castration in Carcinoma of the Breast

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The beneficial effects of oophorectomy as a palliative procedure in advanced mammary carcinoma have been known for more than 60 years (Schinzinger, 1889; Beatson, 1896). With increasing knowledge of the relationship of certain malignancies to hormonal functions, particularly the estrogen-dependent carcinomas of the breast, castration by surgical means or by irradiation of the ovaries has become more widely practiced in the management of metastatic cancer of the breast.

In contrast to the acceptance of castration as a palliative measure in the treatment of advanced cancers, the suppression of ovarian function, either by surgery or by irradiation as a prophylactic method before metastases occur, has been a controversial problem. The majority of publications on this subject have been in disfavor of such procedures, as exemplified by Ackerman and del Regato [1] by the statement: "There is no evidence that sterilization results in the prolongation of life or that the systematic sterilization of operated patients results in prevention of metastases."

However, more recently, an increasing number of investigators have accepted a different attitude. Smith and Smith [2] studied the effect of prophylactic castration on 101 patients operated upon for cancer of the breast. Of these, 60 underwent oophorectomy, and 41 received radiation therapy to the ovaries. As compared with a group of noncastrated patients, the survival rates were higher among the castrates, "the most striking and statistically significant differences being in those with axillary metastases. . . . In the analyses with reference to age, moreover, the difference of the highest significance was between the castrates aged 50 through 59 and the uncastrated controls of the same ages." Although in this group the results following irradiation of the ovaries were not as favorable as those after oophorectomy (40% survival rate in the irradiated groups, as compared with 74% in the surgical groups), they were apparently sufficiently encouraging to lead to the authors' conclusion that "the alternative when surgical castration is refused or contraindicated is adequate ovarian irradiation."

Very favorable results of prophylactic castration were reported by Schönbauer and Schmidt-Ueberreiter [3,4] in 1954 and 1955. Of 205 patients observed between 1941 and 1951, there were 101 alive at the time of the publications; 104 were dead. Of the living, only 16 had active ovaries, whereas 85 were without ovarian function. Of those who died, 85 had functioning ovaries, and 19 had inactive ovaries. In view of these differences in the results, the authors regard prophylactic castration as fully justified.

The importance of oophorectomy in patients with primary carcinoma of the breast and axillary-node involvement at the time of the original surgery is stressed in a recent thorough study by Treves.[5] He found that the survival rates of patients with axillary-node involvement were considerably improved after oophorectomy; in the reported group, irradiation of the ovaries seemed to improve the survival rates only of patients without node involvement. Local recurrences of carcinoma of the breast in this series were observed after bilateral oophorectomy on an average of nine months later than after ovarian irradiation. Pa-

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tients who developed recurrences survived nearly twice as long after mastectomy if ovarian irradiation had been carried out.

Hadfield and Holt [6] compared premenopausal women with carcinoma of the breast treated by radical mastectomy alone with a group of patients in whom radical mastectomy was followed by oophorectomy. The incidence of metastases in the three-to-five-year postoperative observation period was considerably lower in the latter group.

Our Observations

Our own observations comprise a total of 275 women who were below the age of 50 and had been referred to the Tumor Clinic of Michael Reese Hospital during the 10-year period from Jan. 1, 1942, to Dec. 31, 1951. These patients were referred for follow-up examinations after radical mastectomy or, more frequently, for postoperative local x-ray therapy. Sixty-six of these patients were lost for follow-up studies before the lapse of five years; in nine patients it was not possible to determine whether they had functioning ovaries or not. The remaining 200 patients have been observed for a period of 5 to 15 years. All these patients had undergone radical mastectomy for cancer of the breast; at the time of operation there had been no clinical manifestation of metastatic spread beyond the axillary lymph nodes, although there is no proof that these patients had no distant metastases.

There was no selection of patients for consideration of prophylactic castration. Since we felt that suppression of ovarian function might be advantageous in patients with carcinoma of the breast, this procedure has been recommended in the management of all patients up to the age of 50 since January, 1942. The failure to follow our recommendation was due to refusal on the part of the referring physicians, or the patients, or their families. Therefore, the decision to carry out castration was made entirely at random and was not influenced by the status of the primary disease, the age of the patient, or other considerations. The choice of the sterilizing procedure was influenced by the referring physician. Of 78 women who underwent castration, 12 had bilateral oophorectomy, whereas 66 received a tissue dose of at least 1,000 r to each ovary. With several of the younger patients, irradiation had to be repeated in order to suppress menstruation permanently. Four patients who had insufficient radiation and who, for reasons beyond our control, were not subjected to a second course, and 15 other patients who were castrated for palliative purposes after metastases had already occurred, are not considered in the castrated group.

TABLE 1.—*Survival Rates of 200 Women Sterilized in Management of Breast Cancer*

	Castrated		Not Castrated	
	Age Under 40	Age 40-50	Age Under 40	Age 40-50
Survival at the time of investigation	21	25	14	30
Dead within 5 yr.	13	11	20	37
Dead after 5 yr.	6	2	3	18
Alive	21-52.5%	25-68.8%	14-38%	30-35.3%
Total survival 59%			Total survival 36%	

Results

Table 1 shows the survival rates of the observed 200 patients, separated into the castrated and the uncastrated group and into two age groups: those under 40 and those over 40 years of age. Of 78 castrated women, 46, or 59%, were alive at the time of the completion of this survey; of 122 not castrated, 44, 36%, were living. The most favorable results were obtained in the age groups over 40, with a survival rate of 68.8% among the castrates; the poorest results were found in the same age group among the noncastrates, with a survival rate of only 35.3%. In the younger age group the survival rate after castration was 52.5%, as compared with that of 38% without castration.

Of the total number of 200 patients, 81 died within five years after radical mastectomy. Of these 81 patients, the exact date of death is known in 66. Table 2 shows

TABLE 2.—*Length of Survival of Sixty-Six Patients Who Died at a Known Date Within Five Years*

	Castrated		Not Castrated		Total	
	Age Under 40	Age Over 40	Age Under 40	Age Over 40	Castrated	Not Castrated
Dead in less than 1 yr.	0	1	3	8	4.7% [1]	24.4% [11]
Dead in less than 3 yr.	3	5	7	12	38% [8]	42.2% [19]
Dead in less than 5 yr.	8	4	6	9	57.3% [12]	33.4% [15]

the time of their survival after radical mastectomy. They are divided in the same manner as the series in Table 1. Among the 21 castrated women, only 1 (4.7%) died within less than one year, as compared with 11 (24.4%) in the noncastrated group. Of women without ovarian function, 57% lived close to five years, whereas only 33.4% of women with active ovaries survived for the same period of time after mastectomy.

Inasmuch as only 12 of the 78 castrations were done by oophorectomy, no attempt is made to compare the results of surgical procedures with castration by irradiation.

Comment

The patients discussed here represent an unselected group except that only women below the age of 50 were considered; the majority of these patients were still menstruating regularly at the time of treatment, and in all of them some degree of ovarian activity may be assumed. However, since we are more familiar now with the persistent estrogenic activity after menopause than at the time when these patients were originally seen in our clinic, other sources of estrogen production must be considered. It is of interest to note that Smith and Smith [2] achieved the most striking improvements in survival rates in the age group between 50 and 59, causing them to advocate the use of castration in women up to the age of 70 with axillary metastases. Our favorable results in the age group between 40 and 50 (68.8% survival) are also suggestive and seem to indicate that the suppression of ovarian function may be of considerable importance in the later premenopausal, menopausal, and early postmenopausal period. Whether axillary lymph-node involvement, emphasized by Smith and Smith as being important, is of great significance appears doubtful in the light of recent investigations. Wyatt et al.[7] could demonstrate that in over 50% of cases of primary malignant tumors in the medial and subareolar areas of the breast, secondary implants were found in the lymph nodes of the mammary chain; yet less than 15% of this group had axillary metastases. Our own observations on patients with axillary metastases in this group do not include a large enough number for comparison.

The results shown in Table 2 indicate that prophylactic castration significantly delayed the occurrence of metastases and subsequent death in that group which did not survive.

No practical methods to determine the degree of estrogen dependence of carcinomas of the breast in premenopausal women has yet been found which could facilitate the indication for castration. The results of this clinical survey, although comprising only 200 patients, appear to be sufficiently significant—even on a statistical basis—to indicate castration, either by surgical removal or by adequate irradiation of the ovaries, in all women with ovarian activity as soon as feasible after radical mastectomy. Castration also is suggested to all women beyond the menopause who still show signs of estrogen production, as indicated by tests of the vaginal mucosa. It is, of course, known that an appreciable number of women, even after removal of the ovaries, exhibit evidence of extragonadal estrogen production. However, it is not within the scope of this paper to discuss

the physiological and therapeutical implications of this phenomenon.

Conclusions and Summary

Two hundred women below the age of 50 who had been referred to the Tumor Clinic of Michael Reese Hospital after radical mastectomy between Jan. 1, 1942, and Dec. 31, 1951, were followed for a period of at least five years, many of them until the time of completion of this investigation.

Seventy-eight of them underwent prophylactic castration, either by bilateral oophorectomy or by irradiation of the ovaries (with a sufficient dose to suppress menstruation permanently) shortly after radical mastectomy, and before clinical evidence of distant metastases was present. Fifty-nine per cent of these survived more than five years, as compared with 36% of 122 patients who were not castrated.

It was noted that the castration effect was particularly favorable in the age group over 40 years, where a survival rate of 68.8% seems to indicate that castration may be of importance during the early menopause.

Among 66 women who died at a known date within five years after mastectomy, survival of the castrates was longer than that of the women who had functioning ovaries.

It is believed that these observations form sufficient justification for advocation of prophylactic castration in all women with carcinoma of the breast who either are still menstruating regularly or otherwise exhibit signs of ovarian activity.

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Lobar Liver Atrophy Following Ligation of Bile Ducts

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Rous and Larimore[4] produced atrophy of segments of the liver in rabbits by ligation of the corresponding branch of the portal vein. The remaining liver segments developed compensatory hypertrophy, which could be prevented by ligation of the bile ducts. Atrophy of one or more segments of the liver was also produced by ligation of the corresponding bile duct, and compensatory hypertrophy was observed in the unaffected segments.[3,5] Recently, ligation of hepatic ducts has been tried as therapy in cirrhosis of the liver in human patients.[1,5]

The present study was undertaken to confirm the experimental production of atrophy and hypertrophy by ligating of bile ducts with and without ligation of corresponding portal venous branches. Pertinent laboratory examinations and histological studies were carried out.

Materials and Methods

Seventeen dogs, weighing from 6 to 12 kg., were used. Each animal was anesthetized with an intravenous dose of 25 mg. of pentobarbital sodium per kilogram of body weight and prepared for surgery. The abdomen was opened by a midline incision and the hepaticoduodenal ligament exposed. When the bile duct pattern was identified, the ventral layer of the ligament was opened, and one or more branches of the bile duct system was ligated with 00 silk. In some dogs the duct was doubly tied with or without severing between the ligatures; in other dogs, the corresponding branches of the portal vein or the hepatic artery were tied, in addition to ligation of the bile ducts. (Dogs 637, 604, 997, and 1007) Table 1 lists the types of operation for all dogs. Figures 1A and 1B give the two patterns of the bile duct system. Whenever the connection between gallbladder and duodenum had to be interrupted, a cholecystectomy was also performed. No antibiotics or other treatments were given.

TABLE 1.—*Operations on Liver—All Dogs*

Dog No.	Lobe Bile Duct Was Ligated to	Additional Procedure
611	Left lobe	
524	Left and left central lobes	
591	Left, left central, and right central lobes	Cholecystectomy
963	Left, left central, and right central lobes	Cholecystectomy
874	Left, left central, and right central lobes	Cholecystectomy
863	Left, left central, and right central lobes	Cholecystectomy
631	Right lobe	
956	Right and right central lobes	Cholecystectomy
628	Right, right central, and left central lobes	Cholecystectomy
834	Right, right central, and left central lobes	Cholecystectomy
853	Right and left lobes	
637	Right, right central, and left central lobes	Cholecystectomy; ligation of right branch of portal vein
604	Left, left central, and right central lobes	Cholecystectomy; ligation of left branch of portal vein
997	Left lobe	Ligation of left branches of hepatic artery
1007	Right lobe	Ligation of right branches of hepatic artery

The serum levels of alkaline phosphatase, albumin and globulin, and bilirubin were determined. The bilirubin levels were determined by use of the direct and indirect Van den Bergh reactions. The alkaline phosphatase levels were measured by the King-Armstrong method. These laboratory studies were done preoperatively and at weekly postoperative intervals for at least four weeks.

The animals were killed 4 to 35 weeks after surgery. At time of autopsy a careful dissection of the bile duct system was performed and the patency of the bile ducts determined by the use of a dye solution which was injected below the ligatures in an upward direction. The liver tissue from the lobes with impaired and that from the lobes with intact bile drainage were compared by histological examination.

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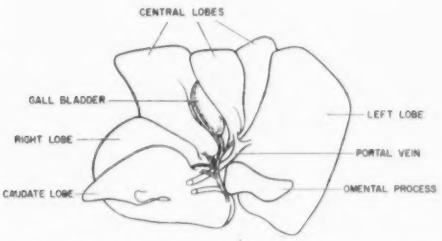

Fig. 1A.—Most typical pattern of bile duct system.

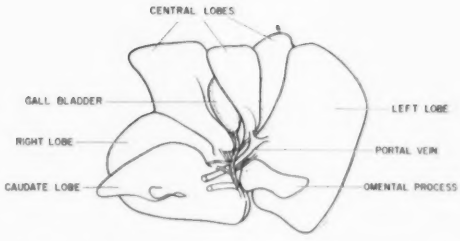

Fig. 1B.—Frequently encountered pattern of bile duct system.

Results

Recovery from surgery was uneventful in all cases. No clinical jaundice was observed. Some animals lost weight during the first two weeks but regained it thereafter.

The alkaline phosphatase level increased considerably in most animals, showing peak values mainly during the second and third postoperative weeks. Detailed values, expressed in King-Armstrong units, are shown in Table 2.

The Van den Bergh reaction yielded indirect readings which slightly exceeded the normal values of 0.1 to 0.4 mg. %. In three dogs higher values, ranging from 0.4 to 1.3 mg. %, were obtained for short periods of time.

The serum protein values remained within the normal range of 5 to 7 mg. %. In a few dogs there was a tendency toward inversion of the albumin/globulin ratio, which never exceeded 1:1.

Autopsies revealed variable formations of adhesions, mainly between the hepatico-duodenal ligament, the ventral border of the liver, and the duodenum. The ligatures were surrounded by fibrous tissue. A tendency toward formation of a new bile duct was indicated by the finding of the ligatures within an ampulla-shaped widening of the duct, the latter as a rule being completely occluded. In two cases we were able to fill the bile duct above the ligature when dye was injected below it.

All lobes exposed to bile stasis were greatly diminished in size. The parenchyma of atrophied lobes was soft, frequently showing a yellowish-brown spotting. The capsule was wrinkled and dull. The remaining lobes were either normal in size or apparently enlarged. The color was normal, or a brighter red than normal. The capsule was smooth and glossy. Figures 2 and 3 illustrate the most typical changes.

TABLE 2.—*Follow-Up Clinical Laboratory Studies: Alkaline Phosphatase Values*

		Postoperative Values				
Dog No.	Preop. Values	1 Wk.	2 Wk.	3 Wk.	4 Wk.	x Wk.
1-611	8.6	25.2	44.5	40.5	29.5	
2-524	8.5	85.2	65.0	54.5	32.8	8.5, 20 wk.
3-591	4.5	107.0	--	--	296.0	28.0, 25 wk.
4-631	7.4	8.3	60.0	20.6	67.5	
5-628	3.9	60.0	--	573.0	156.6	107.5, 23 wk.
6-637	7.6	273.6	174.0	61.2	100.0	8.5, 23 wk.
7-604	2.5	132.1	122.0	104.0	68.3	43.0, 19 wk.
11-859	5.5	22.9	25.8	26.7	19.0	
12-874	12.1	36.0	213.2	154.0	173.8	
13-834	7.3	258.0	754.0	252.6	235.4	
14-863	5.9	364.6	762.0	508.0	539.8	
Average	6.4	131.5	246.4	179.5	156.2	

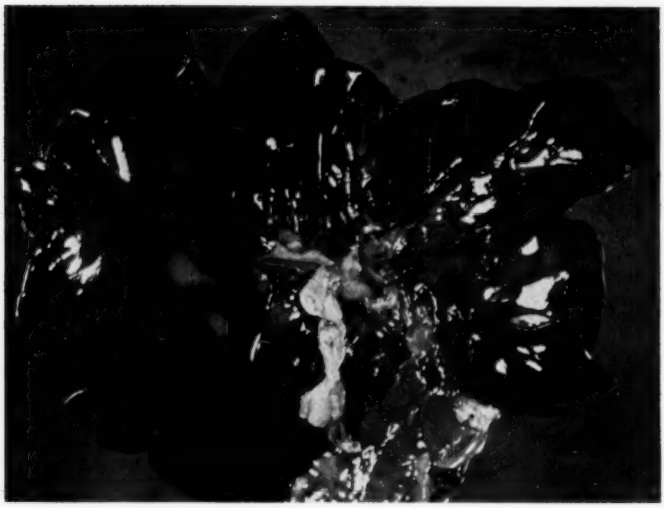

Fig. 2.—Visceral surface of liver from Dog 963. The extrahepatic bile ducts to the left and central liver lobes had been ligated. The right lobe is apparently twice its former size.

Adhesions between highly atrophied lobes and the diaphragm were frequently seen.

Histological Findings

The atrophied lobes showed biliary cirrhosis. There was reduction in size of the lobules with widening of the portal tracts. The widening was due mainly to proliferation of bile ducts, although there was also some increase in fibrous tissue. Bile thrombi were rarely seen. No distinction was possible between the lobes in which the portal vein and the bile ducts had been ligated and the lobes in which only the bile ducts had been ligated. In lobes showing gross hypertrophy no definite microscopic changes were seen.

In one dog killed seven weeks after surgery there was focal and peripheral necrosis of liver cells with polymorphonuclear-leukocyte infiltration. In this animal a small number of inflammatory cells was also seen in the portal tracts of the lobes with intact bile ducts.

Serial liver biopsy specimens were not taken from the dogs allowed to live longer; so the pattern of development of change is not known, but appears similar to that previously reported in prolonged biliary obstruction with little or no infection.[2]

Fig. 3.—Parietal surface of liver from Dog 604. The left branch of the portal vein, and the extrahepatic bile ducts to the left and central lobes had been ligated. The right and caudate lobes are greatly enlarged, and the central and left lobes are atrophied and adhere to each other.

Conclusions and Summary

Atrophy of a liver lobe by ligation of its own extrahepatic bile duct was produced in all cases without endangering the animal's life. However, changes in serum bilirubin and plasma protein were small and temporary, but the serum alkaline phosphatase was greatly elevated in all cases, and this usually persisted for three or more weeks.

The use of ligation of the bile duct to treat portal cirrhosis is mentioned. The probable role of ligation of bile ducts and the concomitant portal vein as a conservative surgical treatment of primary cancer of the liver is to be considered. Although atrophy of the liver cord cells occurs, the small bile ducts appear to proliferate. Therefore, further experiments are necessary to evaluate the effect of this procedure upon both primary hepatic-cell or duct-cell cancer.

Atrophy of segments of the liver in 17 dogs resulted when ligatures were applied to the bile ducts draining the segments, and also when ligatures were applied to branches of the portal vein and the bile ducts. Nonligated segments showed hypertrophy with normal histology. There were no signs of jaundice. Laboratory studies showed extreme elevation of the alkaline phosphatase; serum bilirubin and serum proteins levels were altered to a slight degree only.

Mrs. Theresa Bittner gave technical assistance.

Roswell Park Memorial Institute (Dr. Kraus).

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Radical Subtotal Gastrectomy for Peptic Ulcer Disease

A Clinical and Laboratory Evaluation

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The decision regarding the type of surgical procedure to be done for a patient with peptic ulcer disease is hampered by the difficulty of an intelligent evaluation of the published results of surgery. This is due to the fact that accurate descriptions are often not given of the exact extent of resection or of the nature of the anastomoses performed. It seems valuable, therefore, to continue to examine, by careful clinical studies, certain points which are still unsettled. The one chosen for appraisal here is the effect of the extent of resection on postoperative nutrition and symptoms.

Visick [1] reported on a "measured radical gastrectomy" which removed all the stomach but 3 in. of the greater curvature and 1½ in. of the lesser curvature. Observation [2] of these patients at postoperative intervals averaging 2.6 years showed that 81% had less than 10% weight loss, a figure comparable to that (namely, 87%) for patients having gastrectomy of less extent. No other well-documented series of such extensive gastrectomies has been discovered.

The present paper reports on 80 patients subjected to gastrectomy amounting to between 85% and 90%, as measured by planimetry, and evaluates gastroduodenostomy in this type of resection (Table).

Distribution of Eighty Cases Followed from Three Years to Six Months, Taken Consecutively, with Rare Exceptions

Duodenal ulcer	63
Gastric ulcer	10
Gastric and duodenal ulcer	4
Marginal ulcer	2
Gastritis	1

Procedure

A midline incision is used in all cases, and occasionally the xiphoid process is excised. The stomach is mobilized completely along the greater curvature, the right and left gastroepiploic vessels usually being preserved with the omentum. *All* of the short gastric vessels are divided and the gastrophrenic ligament in part. Care is taken to preserve the branches of the inferior phrenic artery. This phase of the procedure is significant because it is only by so doing that enough mobilization of the stomach is procured to permit one to estimate accurately the extent of resection and, in these cases, to make a pattern for later verification. Furthermore, the proximal remnant is so detached that the final anastomosis, no matter what the size of the remnant or whether gastrojejunostomy or gastroduodenostomy is performed, is tension-free and can be accomplished without difficulty below the costal margin. Its position here remains constant, accounting in part for the postoperative absence of stomal difficulties.

Thereafter, the left gastric vessels are transected posterior to the stomach. At this point the proximal end of the stomach is supported only by the esophagus, a portion of the gastrophrenic ligament, and branches of inferior phrenic artery. The vascular anastomoses in the stomach are so profuse that in all cases there has been an excellent supply remaining from the inferior phrenic artery and esophageal vessels. Ischemic necrosis of the gastric remnant has been reported [7-9] with even less radical resec-

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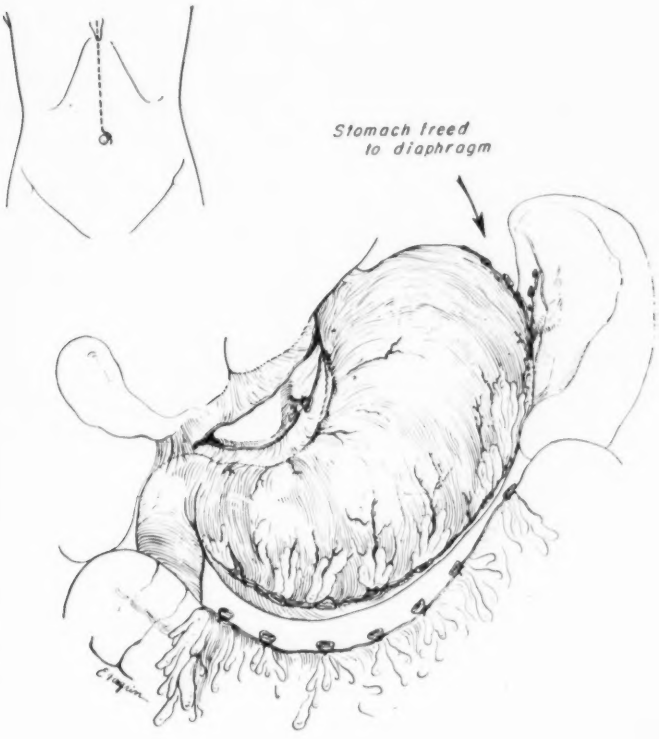


Fig. 1.—Midline incision. Xiphoid occasionally removed. Greater curvature cleared in entirety.

tions, however, so that caution must be used regarding the remaining blood supply.

The stomach is then placed on traction with two lung clamps, and a pattern of broadcloth is made of the anterior surface of the stomach, with the proposed gastric remnant outlined so that by subsequent planimetry it will be possible to estimate the extent of resection.[10]

The stomach remnant is fashioned in the form of a tube by placing a clamp transversely across from the greater-curvature side and preserving 2½ to 4 in. as measured from the esophagogastric junction. All of the lesser curvature is removed, and this side of the remnant is turned in in the usual Hofmeister fashion.

Only after the proximal cuff has been constructed is attention turned to the distal portion of the stomach. The ulcer craters are either excised or excluded in all cases reported. In two-fifths of the cases continuity was restored by gastroduodenostomy. Here a careful Kocher maneuver, freeing up the lateral peritoneal reflection of the second portion of the duodenum and mobilizing the head of the pancreas, is done to allow an anastomosis without tension. The gastrojejunostomies are antecolic, with a 12 cm. afferent loop and the efferent bowel attached to the greater curvature of the stomach (Figs. 1-4).

Postoperative Management

Levin-tube gastric suction is maintained for one day in patients after gastrojejunostomy and four days in those having gastroduodenostomy. Gradually increasing amounts of water and milk are given, and by the sixth day some soft solids are begun. Six equal feedings per day are then started. The patient is told to expect postgastrectomy symptoms (dumping) and is instructed

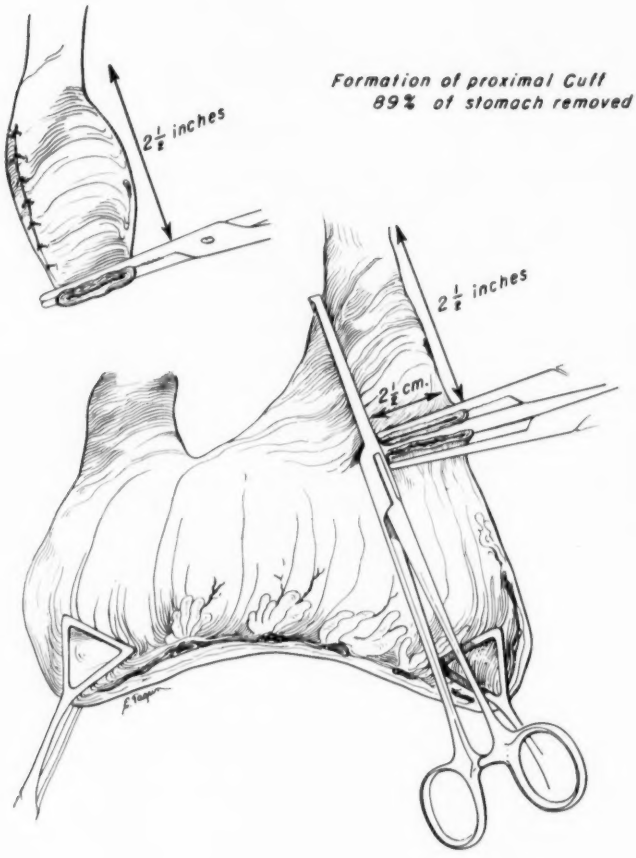


Fig. 2.—Formation and usual measurements of the proximal cuff.

to lie down after eating in the first few weeks postoperatively.

Method of Evaluation

This consists of three parts. First, to determine whether the technical objectives have been attained, planimetry is done on the stomach pattern made during the operation. This gives an accurate estimate of the amount of stomach removed.

Second, to obtain some laboratory evaluation of the patient's need for operation (his peptic potential), to determine the success of surgery in making the likelihood of recurrent ulceration negligible, and to help in following the vicissitudes of his postoperative course, serum pepsinogens are determined.

Third, a continuing clinical follow-up is made, with particular emphasis on postgastrectomy symptoms, weight, and job rehabilitation. Gastrointestinal series are obtained on all patients with any abdominal complaints, and hematocrit and hemoglobin determinations are done routinely after two years' follow-up. Follow-up evaluation has been done by means of clinic visits rather than questionnaires in all cases.

The only one of these methods which needs further elaboration is the test for serum pepsinogen. If renal function is normal, the serum level of this enzyme has been determined to be a good indication of the peptic potential of the gastric mucosa. This is usually, but not necessarily, parallel to the acid output.[22] The laboratory test

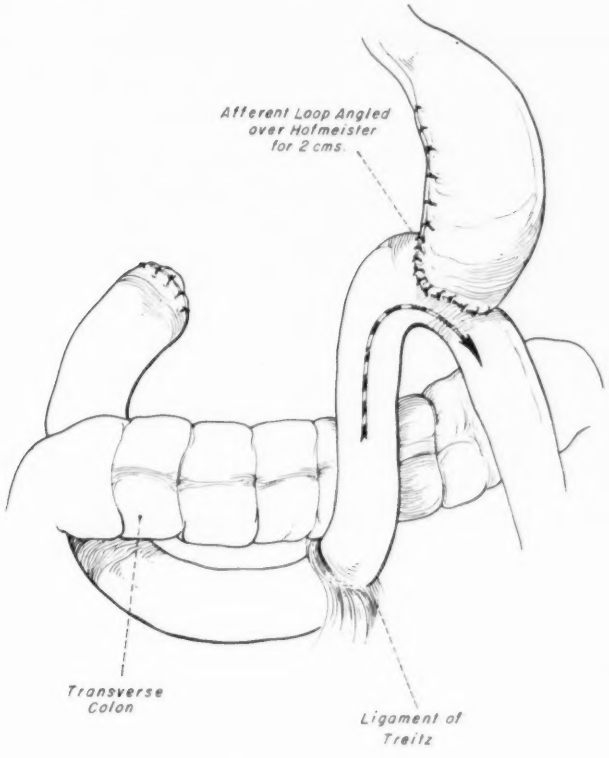


Fig. 3.—Method of construction of gastric jejunostomy. Afferent loop is 12 cm. as measured from the ligament of Treitz.

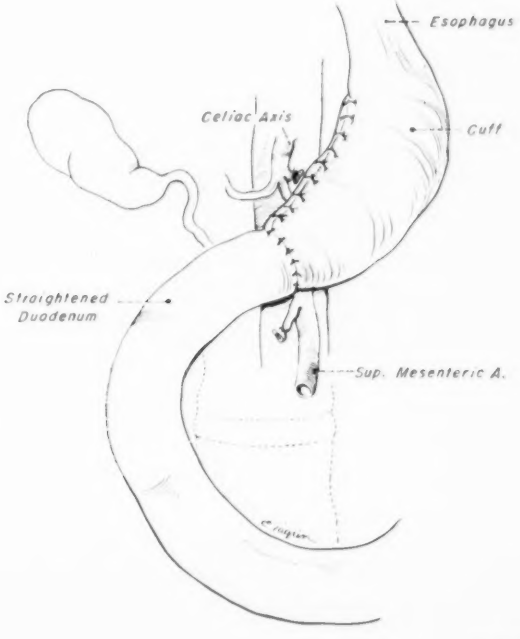


Fig. 4.—Method of construction of gastroduodenostomy.

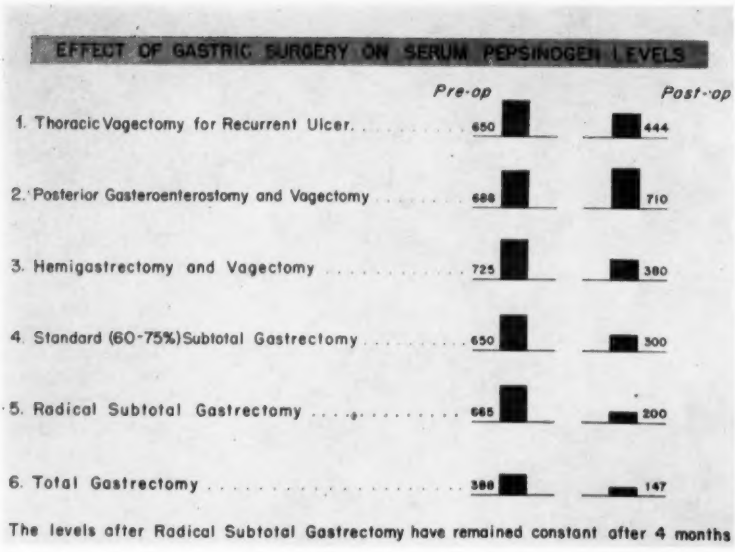

EFFECT OF GASTRIC SURGERY ON SERUM PEPSINOGEN LEVELS
Pre-op
Post-op
1. Thoracic Vagectomy for Recurrent Ulcer. 650 444
2. Posterior Gasteroenterostomy and Vagectomy 688 710
3. Hemigastrectomy and Vagectomy 725 380
4. Standard (60-75%) Subtotal Gastrectomy 650 300
5. Radical Subtotal Gastrectomy 665 200
6. Total Gastrectomy 388 147
The levels after Radical Subtotal Gastrectomy have remained constant after 4 months

Fig. 5.—Graph illustrating pre- and postoperative values for serum pepsinogen with various surgical procedures.

for serum pepsinogen as modified by Mirsky and used in our laboratory has been described.[21] It is reliable and has a coefficient of variation of only 4%. Much work has to be done over several more years to determine its place in the evaluation of gastric secretory activity. We are trying to determine its value in estimating the virulence of the ulcer tendency in a given patient and hence the type of treatment indicated, as well as its use in the determination of the adequacy of treatment.

In our cases three preoperative determinations have been done and additional ones have been made at each postoperative visit. We have become accustomed to expect a level of about 200 tyrosine units to be consistent with good protection against recurrent ulcer disease (Fig. 5). No recurrences have been noted from any type of ulcer surgery if these values are attained. Vagectomy does not lower the serum pepsinogen to this range (Fig. 5). The determination is simple from the patient's point of view, since it involves only a venipuncture and can be done, irrespective of meals, at any time of the day. Following partial gastrectomy, when aspiration techniques for determination of gastric secretions are so unreliable because of contamination by bowel contents, the serum pepsinogen test has the same reliability in the estimation of peptic potential that it had preoperatively.

Results

A total of 80 patients have been followed for six months to three years after radical subtotal gastrectomy. There has not been any selection in this group with the exception of the rare patient who has some factor making for a poor surgical risk, such as heart disease or age beyond the seventh decade. The type of peptic ulcer disease present in the cases in this series is broken down in the Table. Gastroduodenostomy has been performed in 32 instances and gastrojejunostomy in 48. There has been no operative mortality.

The early postoperative morbidity has been comparable to that in other closely supervised series of gastrectomy patients. Hospitalization is usually for 15 days after operation. There have been no stomal prob-

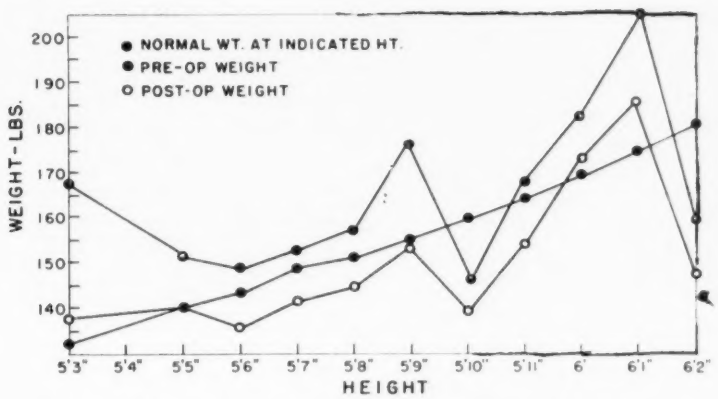


Fig. 6.—Weight curves, pre- and postoperative, compared with the average.

lems, requiring retubation or reoperation. There have been three instances of postoperative pancreatitis, in two of which death was narrowly averted.

The late postoperative morbidity, that is, after six months, in this group must be evaluated in several ways: ulcer recurrence, nutritional status, postgastrectomy ("dumping") symptoms, and success of rehabilitation.

There have been no ulcer recurrences.

As in most series following subtotal gastrectomy, there is in this one a reasonable, average weight loss (Fig. 6). There were several instances, however, when the preoperative weight level was exceeded postoperatively. Criteria were established to define the designation "nutritional problem." To avoid this category, postoperative weight had to be maintained within 10% of the lower of the following values: (1) the patient's average preoperative weight (not the immediate preoperative weight noted at hospitalization, which may often be out of line with what the patient would consider his "usual weight"), or (2) the lowest figure in the "Metropolitan Life Insurance Company Statistical Bulletin" for the particular patient's height. In the present series there is one patient regarded as a "nutritional problem."

Postgastrectomy symptoms, commonly known as "dumping," were graded 1 to 4, as follows: 1, no symptoms; 2, few symptoms; 3, symptoms causing constant annoyance (patient has to lie down postprandially); 4, symptoms that are incapacitating. These symptoms include postprandial sweating, palpitation, fullness, diarrhea, nausea or vomiting, and weakness. One of the best clues to the severity of the problem in a given case is whether or not the patient feels compelled to lie down because of it. Almost invariably patients can be found to have some of these symptoms in the early postoperative course. This is true after any type of gastric surgery in which the pylorus is removed or bypassed. The late results in this regard in the present group of patients are summarized in Figure 7. A total of 95% of these patients had few, if any, postgastrectomy symptoms (Grades 1 and 2), and there were none with incapacitating symptoms. It is to be noted that 44% of those patients with gastroduodenostomy, as opposed to 23% of those with gastrojejunostomy, had *no* symptoms related to the postgastrectomy state. This bears out the clinical impression in this group, expressed by other authors, that the former, or so-called Billroth I anastomosis, produces a better functional result. It is our conviction, however, that nothing less than an 85% gastric resection should be done for *duodenal ulcer* disease if a gastroduodenostomy is to be performed, because of the

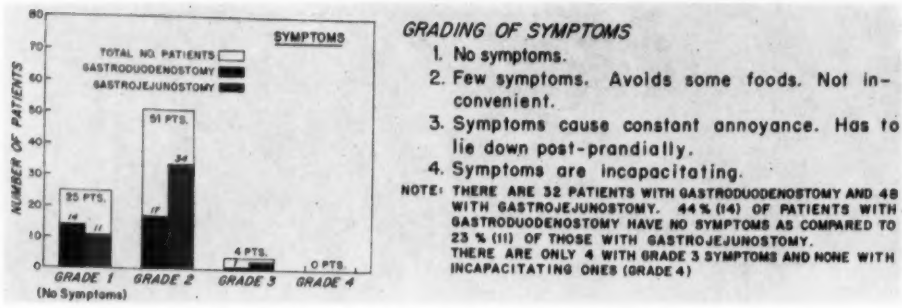

SYMPTOMS
TOTAL NO. PATIENTS
GASTRODUODENOSTOMY
GASTROJEJUNOSTOMY
NUMBER OF PATIENTS
25 PTS.
51 PTS.
4 PTS.
0 PTS.
GRADE 1
(No Symptoms)
GRADE 2
GRADE 3
GRADE 4
GRADING OF SYMPTOMS
1. No symptoms.
2. Few symptoms. Avoids some foods. Not inconvenient.
3. Symptoms cause constant annoyance. Has to lie down post-prandially.
4. Symptoms are incapacitating.
NOTE: THERE ARE 32 PATIENTS WITH GASTRODUODENOSTOMY AND 48 WITH GASTROJEJUNOSTOMY. 44% (14) OF PATIENTS WITH GASTRODUODENOSTOMY HAVE NO SYMPTOMS AS COMPARED TO 23% (11) OF THOSE WITH GASTROJEJUNOSTOMY. THERE ARE ONLY 4 WITH GRADE 3 SYMPTOMS AND NONE WITH INCAPACITATING ONES (GRADE 4)

Fig. 7.—Results in terms of postgastrectomy symptoms.

high percentage of recurrence of ulcer when this rule is not adhered to.[10-16]

The final summation of the results in these patients, which includes their rehabilitation in regard to work and play, is shown in Figure 8. These results are graded 1 to 4 as follows: 1. Normal. No evidence of the postgastrectomy state can be observed in the history or through physical examination. 2. Good. The patient has some symptoms, perhaps "dumping," or late-afternoon fatigue. He avoids some foods. He is happy and does his usual work, however. 3. Fair. The symptoms are more marked. The weight is lower than usual. Fatigue is a prominent complaint. The patient looks and feels under par. He is doing his usual work, however, but with less than normal capacity. It should be noted that even in this group the patients claim to be happy and to be glad they had the operation performed 4. Poor. Here would be grouped patients with severe nutritional problems or incapacitating dumping. They would not be employed—not rehabilitated.

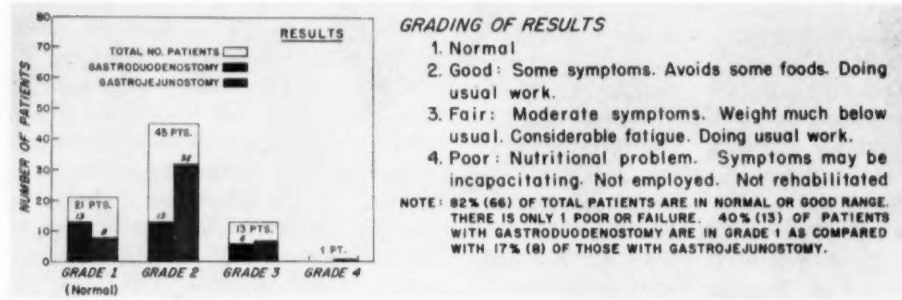
As Figure 8 shows, 82% of the results in this entire series are "good" or better according to these criteria, rates which compare relatively favorably with those in most reported series of gastric surgery for peptic ulcer disease.[7] There was only one "poor" result. The patients with gastroduodenostomy seemed to do best.

All patients followed for two years or more have had hematocrit determinations, and no cases of anemia have been discovered. None have needed to be on supportive iron or cyanocobalamin (vitamin B_{12}) therapy as yet.

Comment

The impression gained from the preliminary review of these patients is that the nutritional results are comparable to those in which less radical techniques were used. The incidence of early nutritional problems is no higher. The follow-up rate here has

Fig. 8.—Over-all results.


RESULTS
TOTAL NO. PATIENTS
GASTRODUODENOSTOMY
GASTROJEJUNOSTOMY
NUMBER OF PATIENTS
21 PTS.
45 PTS.
13 PTS.
1 PT.
GRADE 1
(Normal)
GRADE 2
GRADE 3
GRADE 4
GRADING OF RESULTS
1. Normal
2. Good: Some symptoms. Avoids some foods. Doing usual work.
3. Fair: Moderate symptoms. Weight much below usual. Considerable fatigue. Doing usual work.
4. Poor: Nutritional problem. Symptoms may be incapacitating. Not employed. Not rehabilitated
NOTE: 82% (66) OF TOTAL PATIENTS ARE IN NORMAL OR GOOD RANGE. THERE IS ONLY 1 POOR OR FAILURE. 40% (13) OF PATIENTS WITH GASTRODUODENOSTOMY ARE IN GRADE 1 AS COMPARED WITH 17% (8) OF THOSE WITH GASTROJEJUNOSTOMY.

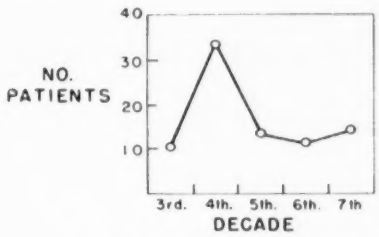


Fig. 9.—Age distribution of patients.

been 95% (80 out of 84 cases); the remaining 4 patients have been contacted by mail or telephone, but not seen.

In the present series, 26% of the results were *normal* and 56% *good*—a total of 82% in these categories. Less than 2% were failures, and 16% were fair. Only 5% of the series had significant dumping symptoms. This is more noteworthy when one considers the relative youthfulness of the patients[18] (Fig. 9).

Much more follow-up time must elapse before one may draw any final conclusions from this group of patients. Further nutritional problems may appear, and, particularly, anemia may develop. Certainly, it is not the purpose of this paper to advocate the use of this radical procedure in all patients with peptic ulcer disease coming to surgery. Sufficient time has passed to permit one to say that, if there are indications of particularly virulent peptic ulcer disease, radical gastrectomy is a reasonable way in which to obtain a good result.

At present we recommend radical gastrectomy to be done on patients who are good risks if the serum pepsinogen is 600 tyrosine units or over. Since there is good correlation between poor postoperative weight gain and poor preoperative eating habits (a closer relationship than between postoperative weight status and body habitus), we tend to regard as poor risks patients who do not enjoy eating, are apt to omit meals, and are very "finicky" about their food.

The literature gives ample proof[14,15] that the recurrence rate after a standard gastrectomy for duodenal ulcer disease with Billroth I anastomosis is prohibitively high. However, these results suggest, though the length of follow-up is too short to be conclusive, that if sufficient mucosa is removed to lower the serum pepsinogen to a level of about 200 tyrosine units, recurrences will occur here as rarely as with the gastrojejunostomy.* Gastroduodenostomy is a better procedure as far as postoperative results are concerned, because 44% of the patients with this anastomosis in this series had no symptoms, as apposed to 23% of those with gastrojejunostomy, and 40% of the former, as compared with 17% of the latter, had Grade 1 results. The Billroth I anastomosis can usually be accomplished safely, and more rapidly than the other.

The serum pepsinogen level is a good indication of the status of the peptic potential. Providing the renal function is normal, this test will give a reproducible figure which will indicate the degree of hypersecretion.[21] Radical gastrectomy should lower the pepsinogen to the 200 tyrosine unit level. Marginal ulcers occurring in patients after other procedures or from other hospitals have been associated with levels above 300, usually near 500, tyrosine units.

The results in the present series seem to indicate that the "storage capacity" of the larger gastric remnant of a 50% to 70% gastric resection has little effect on the results, for the more radical resection seems to measure up well with those less radical.[19,29] The truth seems to be that once one has removed 50% or more of the stomach, the organ no longer functions as a reservoir, because of rapid emptying, so that little is gained nutritionally or in regard to dumping incidence by the larger gastric remnant.

Some recent articles[3,6] attempt to associate the extent of gastric resection with the severity of postoperative nutritional and dumping problems. Our results are in disagreement with these attempts and the con-

* There are no known recurrences, after four and one-half years, at the time of writing.

ventional feelings regarding this problem. The other reviews are difficult to judge because the methods of estimating the extent of resection have not been accurate, and often the cases have been reviewed from records rather than from personal follow-up.

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Routine Cardiac Monitoring During Surgery and a Cardiac-Arrest Team in a General Hospital

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The problem of cardiac arrest plagues hospitals throughout the country. It has been estimated that there are 10,000 cases a year in the United States.[1] Efforts are being made in many hospitals to reduce the incidence and to increase the survival rate by stressing methods of prevention and therapy; nevertheless, the mortality rate of cardiac arrest remains about 70%.[2]

Survival depends on whether the heart can be restarted and whether death from cerebral anoxia can be avoided. The two prime factors in survival, therefore, are speedy diagnosis and skillful treatment. It is interesting to speculate what the survival rate might be if therapy were perfectly handled.

It has been shown that hearts of dead animals and humans can be restarted as long as six hours after death.[3] Since approximately 50% of cases of cardiac arrest occur in persons with "normal" hearts, it would seem, therefore, that these patients should all recover with proper treatment. The possibility of recovery in patients with heart disease is not as good. We have found that in a study of 205 cases of cardiac arrest in the literature, there were 46 with proved heart disease.[4] Of these, 20% recovered. For that reason we feel that 20% is a minimal recovery rate for patients with heart disease. Therefore, in combining the figures for normal and for abnormal hearts, we should anticipate an over-all survival rate of at least 60%.

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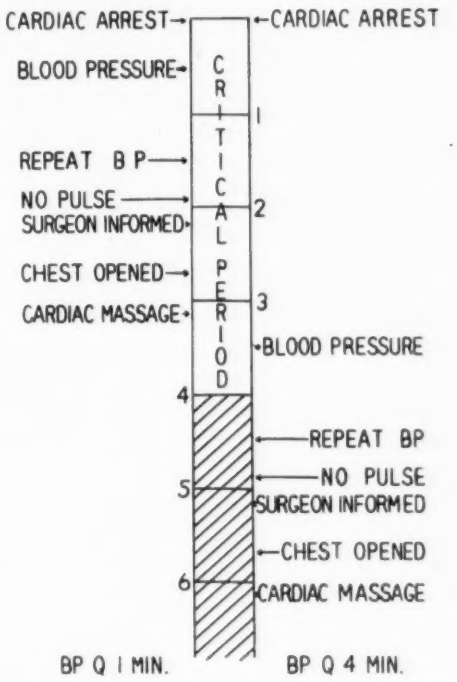

Fig. 1.—Diagram illustrating the urgency of prompt diagnosis and therapy in cases of cardiac arrest (see text for details).

Why, then, is the national survival rate only 30%? The answer undoubtedly is delay in treatment or lack of treatment.

Let us set up a hypothetical clinical situation where conditions are relatively good (Fig. 1). Let us assume that the anesthetist is exceptionally vigorous, and takes the pulse and blood pressure every minute. When he finds the blood pressure unobtainable, his first reaction will be to recheck it. Since it takes about 30 to 40 seconds to take each blood pressure, almost two minutes will have elapsed before the surgeon hears the bad

news. During the panic of the next 30 or 40 seconds, the surgeon will probably lose time in trying to find the nonpulsating aorta and in questioning and directing the operating-room team. He will then open the chest, and cardiac massage may be initiated at a little over three minutes.

Irreversible cerebral damage occurs after three to four minutes of cerebral anoxia; in the hypothetical situation described, the patient may, therefore, recover, and have only transient cerebral damage.

Unfortunately, however, it is far commoner that the anesthetist check the blood pressure every four to six minutes, and, assuming that arrest occurs just after a reading and that the subsequent events follow as described, active therapy will not be instituted before six to eight minutes, at which time irreversible cerebral damage will have occurred. The situation is, of course, even worse when cardiac arrest occurs in the cystoscopy room, recovery room, or in other out-of-the-way places, because an equipped team is usually not available and valuable time is lost.

Despite the somewhat dramatic description of the type of catastrophe presented here, those who have experienced such an event will realize that the picture is not far from the actual truth.

Organization of Program

In an effort to reduce the mortality rate of cardiac arrest at the Newark Beth Israel Hospital, a threefold program was instituted, consisting of (1) education, (2) organization, and (3) the use of cardiac monitor alarms.

A series of lectures was given to the attending staff and house staff on the principles of prevention and treatment of cardiac arrest. The lectures are repeated yearly. In addition, a group of surgeons gave animal demonstrations on the proper technique of cardiac massage.*

* Dr. B. B. Bergman, Dr. L. Gilbert, Dr. V. Parsonnet, and Dr. D. Wiener.

Simultaneously, the house staff was organized into a cardiac-arrest team, the members of which are trained in the various phases of treatment. A page system is used with the call "Dr. Pacemaker to——— Room, stat." This has proved effective in getting at least five members of the team to the patient within two minutes, and is particularly valuable when the cardiac arrest occurs somewhere other than in the operating room (where a sufficient number of trained personnel are usually at hand). The "Dr. Pacemaker" page also serves to call any interested house-staff members, an anesthetist, and an electrocardiography technician, who obtains permanent tracings.

The operating rooms, delivery rooms, fracture room, and cystoscopy room are provided with emergency trays containing the essential materials for prompt therapy (Table 1). The operating-room cart contains sufficient material for complete treatment, including drapes, intubation equipment, and a thoracotomy-closure set (Fig. 2; Table 2).

TABLE 1.—*List of Equipment and Drugs on the Emergency Trays in the Minor Operating Rooms*

1 oral airway
1 Tuffier rib retractor
1 #4 knife handle with #20 blade
2 6 in. needles (#18 and 21)
2 1½ in. needles (#21)
2 10 cc. syringes
2 2 cc. syringes
1 vial Epinephrine 1:1,000
2 ampules 2% procaine HCl
2 ampules procainamide HCl
2 ampules 10% calcium chloride
1 vial atropine

Cardiac monitor-alarms were provided for each operating room, as well as the cystoscopy room and the postoperative-recovery room. The apparatus was attached to all patients when they were put on the operating table, except to those who were to receive local anesthesia. The monitor remained in use until the patient was moved to the recovery room. If indicated, another monitor was then applied until the patient had reacted fully.

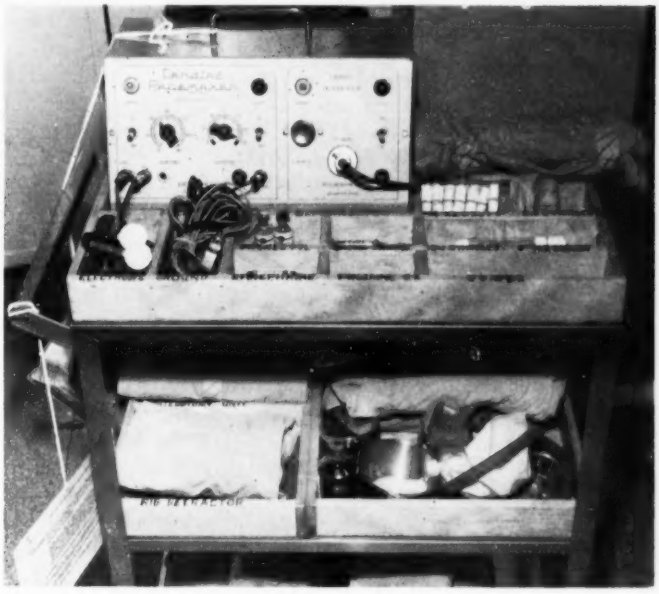

Fig. 2.—Cardiac-arrest cart, showing compartments for specific equipment, drugs, and pacemaker-defibrillator (Table 2). This unit is kept in the corridor of the operating suite.

TABLE 2.—*List of Equipment and Drugs on the Major Emergency Cart* *

Top Shelf	Middle Shelf
1 defibrillator with pacemaker unit with all attachments	1 rib retractor
1 scalpel with blade	1 phlebotomy unit
2 6 in. needles (#18 and 21)	4 gowns
2 1½ in. #21 needles	4 pr. gloves, 7½ size
2 10 cc. syringes	1 jar alcohol sponges
2 2 cc. syringes	1 bottle tincture benzalkonium (Zephiran)
4 ampules calcium chloride 10%	1 oral airway
2 ampules procaine 2%	1 positive-pressure oxygen mask and oxygen-tubing attachment
1 vial procainamide	1 pack sterile towels
1 vial epinephrine 1:1,000	1 laryngoscope
1 vial atropine	2 endotracheal tubes

Bottom Shelf

Sterile thoracotomy closure tray with the following equipment:

1 #4 knife handle with blade	1 rib approximator
2 dissecting scissors	2 small retractors
2 tissue forceps with teeth	1 package small abdominal needles
1 tissue forceps without teeth	1 package gauze sponges
2 needle holders	1 sponge forceps
9 curved Crile clamps	1 small solution basin
4 Allis clamps suture material	4 towels
4 towel clips	6 6×6 in. sponges
1 suture scissors	2 plain sheets

* See Figure 2

Results

With the use of the monitors much valuable information has been obtained. Various arrhythmias were observed, and their rate of occurrence was found to be proportional to the degree of estimated surgical risk. Of 534 consecutive cases, arrhythmias were noted in 11% of good-risk patients, in 20% of fair-risk patients, and in 61% of poor-risk patients. An effort is always made to correct the arrhythmia as soon as it occurs. Sinus bradycardia is common and usually can be corrected with intravenous atropine. Some of our surgeons are now using larger doses of atropine preoperatively as a prophylactic measure.

Since the time that monitors have been used on all patients (except those under local anesthesia alone), we have had three cardiac arrests; in two patients the chest

TABLE 3.—*Comparison of Survival Results With and Without the Use of a Monitor-Alarm in Thirty-Seven Patients (1952-1957)*

	No. of Cases	Survivals
Monitor-alarm not used	28	6 (21%) *
Monitor-alarm used	9 †	4 (44%)
Total	37	10 (27%) *

* Including one decerebrate patient.
† Mostly poor-risk patients.

was opened within 20 seconds of standstill (Table 3). Two of these three patients survived; one recovery followed pounding on the sternum and the other after cardiac massage. In the third case, despite the promptness of therapy, spontaneous cardiac activity did not return. Before that, with the use of a single monitor applied to poor-risk patients only, there were two survivals out of six cases of arrest. This represents a 44% survival rate in nine patients in whom the monitor alarm was used. Our premonitor statistics consist of 28 arrests with 22 deaths and 1 decerebrate patient, or a survival rate of about 20%.

In addition to achieving a greater survival rate with the use of monitors, we also feel that a number of arrests have been averted by prompt therapy. For example, in two cases sudden, severe bradycardia, of 20 per minute, was corrected with intravenous atropine; both these patients had had recent myocardial infarcts. In another instance a sudden ventricular tachycardia led to the discovery of a kinked endotracheal tube; the tachycardia had not yet been observed by the anesthetist.

Comment

The educational and organizational arrangements described so far have been instituted in many hospitals throughout the country and are more or less standard in their details. The unique feature of our program is the use of a cardiac monitor-alarm on every anesthetized patient.† To our knowledge, the Newark Beth Israel Hospital is the first hospital to report the use of a monitor-alarm in every operating room on every patient. We feel that it is necessary to use the monitor on patients with normal, as well as with abnormal, hearts, because 50% of cardiac arrests occur in "normal" patients, and the occurrence is therefore unpredictable.

† We use an Electrodyne PM-65 with electrocardioscope, and seven of the Electrodyne Cardiac Alarm #54 model (Electrodyne Co., Inc., Norwood, Mass.).

A large selection of monitors is available. Most of them work on a combination of visible and audible impulses, triggered by the highest peak of the QRS complex of the electrocardiogram. After a careful study of six of the currently available instruments, we felt that the one indispensable feature must be an alarm that sounds at the cessation of cardiac activity. Instruments without alarms were repeatedly found to be unsatisfactory, because the mere cessation of the monotonous clicking frequently went unnoticed for some time, especially if suction apparatus was in use or other distracting noises were present. The machines were also checked for ease of application of the electrodes (we prefer a single chest strap) and for freedom from interference by electric circuits, muscular movements, or rubbing of metal retractors.

Various models feature additional equipment, such as an oscilloscope to allow constant observation of the electrocardiogram, built-in jacks to be attached to an electrocardiograph when a permanent record is desired, automatic pacemakers, and explosion-proof housings.

The automatic pacemaker is an interesting feature, but we believe that its use is contraindicated in operating-room cardiac arrests. It has been our observation that the pacemaker is frequently ineffective in producing a contraction in the anoxic heart at standstill, and invaluable time may be lost by trying a pacemaker or a transthoracic defibrillator, by pounding the chest, or by needling the left ventricle. It is our conviction that the proper treatment for cardiac arrest is immediate thoracotomy and cardiac massage.

Although the primary theme of this report has been the necessity for prompt therapy in cases of cardiac arrest, it is our opinion that the preventive measures are still more important. A retrospective scrutiny of circumstances at the time of arrest will almost always uncover several unfavorable conditions, such as undue anoxia, excessive sedation, or visceral traction. Moreover, in

going back further, one may find a number of predisposing factors that were not given proper attention; these may include, for example, uncorrected anemia, adrenal exhaustion, or electrolyte imbalance. It is the attention to detail beforehand that is likely to accomplish a decrease in the over-all incidence of cardiac arrest. Should cardiac arrest occur despite all reasonable care, then the plan outlined here will afford a maximal chance for recovery.

Conclusion

On the basis of our experience, we find that cardiac monitor-alarms used on all anesthetized patients are a great asset in the prevention and treatment of cardiac arrest. They allow us to recognize and treat arrhythmias as soon as they occur and alert us to the fact that arrest may be impending. Even in the absence of premonitory signs, when cardiac arrest occurs, we are made aware of it unequivocally and at once, and thus gain time—the most important ingredient of successful therapy.

202 Clinton Ave. (5).

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Treatment of Pilonidal Sinus by Primary Closure

A Seven-Year Study

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The surgical treatment of pilonidal sinus has remained controversial. Reports from various institutions have shown a wide variation in the incidence of wound-healing complications, and follow-up studies have similarly shown a wide variation in the recurrence rate. Several years ago a technique of excision and primary closure was described, and preliminary follow-up studies were reported.[14] Our purpose now is to bring this study up to date and present the results of long-term follow-up study.

The operation which we have used throughout this seven-year study is a modification of the bilateral musculofascial-flap procedure described by Holman[5] in 1946. Our technique differs from the one described by Holman in that we have used no buried suture material, wound closure has been obtained by means of removable far-and-near sutures[2,15] of stainless steel inserted through fascia and subcutaneous tissue, as well as skin, and the wounds have been closed without drainage. Holman gave credit to Pope for having first brought his attention to the principle of using gluteal fascia for wound closure. Pope,[10] however, advised the use of a unilateral flap, and he described the successful application of this method in a large series of cases.[11] Ziegler[16] also had described a unilateral-flap procedure. Miscall and Holder[8] and Shute et al.[12] had previously described successful operations in which bilateral equal flaps of gluteus maximus muscle were mobilized. The difference between their respective operations and the one later described by Holman is that they turned the inner divided ends of the gluteal fascia medially and sutured them to each other in the midline. The lateral cut edges of the gluteus maximus were then brought together in the midline as a second layer, as in the method described by Holman.

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From the Veterans Administration Center, Department of Surgery.

Clinical Material

One hundred forty-five patients with symptomatic pilonidal sinus were admitted to the hospital during the seven-year period covered in this study. One hundred twenty-five unselected patients were treated by excision and primary closure with the technique described. In 22 patients miscellane-

TABLE 1.—*Surgery of Pilonidal Sinus: Seven-Year Study in 145 Patients* *

Excision and primary closure (Musculofascial flap operation) (Secondary operations—7 pts.)		125	
Miscellaneous operations		22	
Excision and partial closure (skin to fascia, McFee)	10		
Simple closure	4		
Marsupialization (Bule)	3		
Excision and packing	2		
I & D † (only)	3		
Miscellaneous group: Analysis as to suitability for treatment by primary closure			
1. Suitable for primary closure			6
2. Suitable for primary closure after prior therapy for acute infection)			9
3. Unsuitable for primary closure			7
Extensive perianal involvement		4	
Extensive lateral involvement		2	
Extensive sacral involvement		1	
Suitable for primary closure (95% of total admissions)			138

* Twelve participating surgeons.

† Incision and drainage.

ous operative techniques were carried out. The primary-closure operation was technically feasible in many of these patients and would have been a satisfactory procedure if used (Table 1). From personal knowledge of the great majority of these patients and from a study of their records it is felt that the primary-closure technique was unsuitable because of extensive sacral, perianal, or lateral involvement in only 7 of the 145 patients. In other words, primary closure could have been carried out in 95% of all the patients with pilonidal sinus admitted to the hospital during this seven-year period. It should be emphasized that during this study an attempt was made to carry out the primary-closure operation in all patients admitted to the hospital with pilonidal sinus in a consecutive and unselected fashion in order more truly to determine the suitability of this particular technique of primary closure as an operative approach.

Fig. 2.—Wire sutures have been partially tightened and skin sutures applied.

Fig. 1.—"Far-and-near" sutures of 00 cable wire have been inserted, and the wound is ready for closure.

Of the group of 125 on whom primary closure was carried out, 52 patients, or 41.6%, had had previous surgical treatment for their disease. Definitive surgery had been carried out on one or more occasions in 31, or 24.8%. Incision and drainage only had been carried out on one or more occasions in 21, or 16.8%. Forty-one patients, or 32% of the total, showed evidences of acute infection on admission to the hospital, as characterized by erythema, tenderness, induration, or frank abscess. Incision and drainage was carried out preoperatively in 15 of the 41. Definitive surgery of en bloc excision and primary closure was then carried out after intervals of from one week to two months following incision and drainage. Conservative treatment, consisting of warm applications, sitz baths, and chemotherapy, was carried out in the remainder.

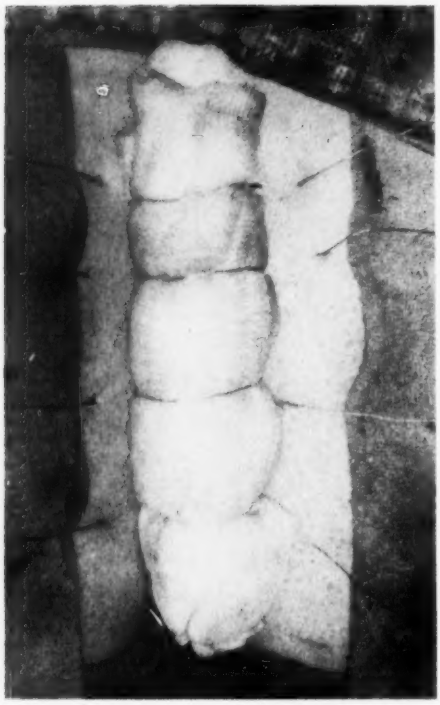


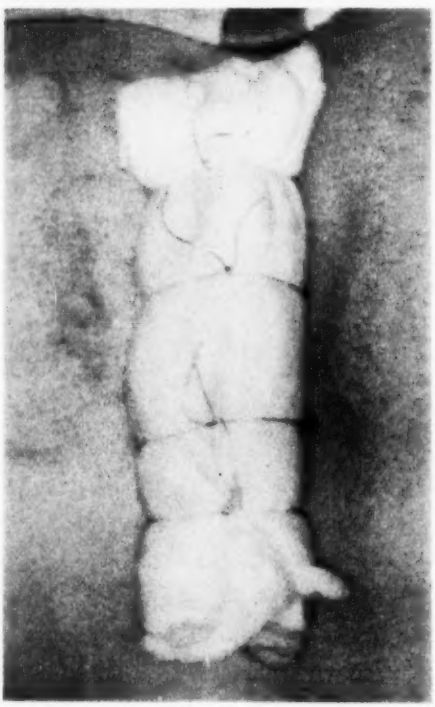
Fig. 3.—This photograph shows application of the innermost gauze roll under the "near" wire loops.

Definitive surgery was then performed when it had become apparent that all cellulitis had subsided and that purulent discharge had decreased to a minimum.

Technique of the Operation

The lesion with all its ramifications is excised en bloc by means of an elliptical incision, which is carried straight down to the sacrococcygeal fascia. Undermining of the subcutaneous tissue is avoided. Hemostasis is obtained by means of hot saline packs and electrocoagulation. Several ligatures of absorbable suture material are occasionally needed. Musculofascial flaps are then developed in the manner described by Holman, and the wound is then closed primarily with far-and-near pull-out wires of stainless steel, either 00 multiple strands or 30-gauge single strands (Figs. 1 through 4). Care is taken that the sutures are inserted through both skin and fascial layers at equal distances from the point of the respective incision in each layer (Figs. 5 and 6). A bite is also taken in the sacrococcygeal fascia. With this type of suture the fascial layers are brought together in the midline almost as easily as the subcutaneous tissue and skin, and all dead space is effectively obliterated. Before closure of the wound, the wound is irrigated first with saline and then with an antibiotic solution. The skin is then meticulously closed, and the far-and-near sutures are tied over two gauze rolls. A separate strip of gauze is first drawn under the innermost wire loops, and a second gauze roll is then placed on top, and under the second row of wire loops, which are then tied. Care is taken to express all fluid out of the wound before the gauze rolls and pressure dressing are applied to the wound. Postoperatively the patient is given clear liquids by mouth for

Fig. 4.—The wire stay sutures have now been tightened over the outermost gauze roll.



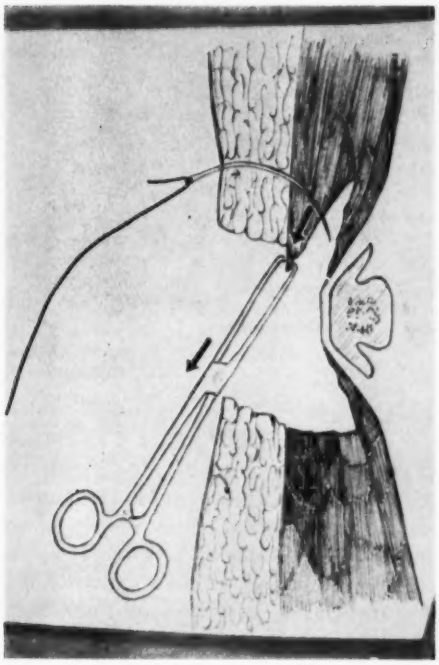


Fig. 5.—Allis clamps are applied to the gluteus fascia, and traction is applied so that the stay sutures can be inserted through both skin and fascia at a point equidistant from the site of incision in each layer.

the first several days, and bowel movements are prevented by means of a low-residue diet and camphorated opium tincture U. S. P. (paregoric). The patient is made ambulatory progressively, but is not permitted to sit down until after the wound is healed. All sutures are removed on the eighth or ninth postoperative day, and the patient is then ready for discharge.

Wound Healing

Primary wound healing was obtained in 111 of the 125 patients, or 88.8%. In 14 patients, because of either hematoma or infection, it was necessary to reopen the wound (Table 2). These wounds healed in an average time of six weeks. The minor wound-healing complications required little, if any, therapy and healed rapidly. These imperfections in wound healing, which cannot properly be called wound-healing complications, have been listed for the sake of completeness and to lay further emphasis on the necessity for obtaining a meticulous and secure closure of skin and subcutaneous tissues. Of the 125 operations, 61 were carried out by us. In this unselected series there was only one infection (1.6%), and there was no hematoma.

Follow-Up Studies

Follow-up studies have been carried out in 121 of the 125 patients (Table 3). Four of these patients have been lost to follow-up. Half of the patients in this series have been followed for more than a year and nine months. Out of the total of 125 patients, 102 have been followed for more than 18 months. There were 13 recurrences, and all of these were noted within less than 18 months after the operation. Further surgery was carried out in nine patients (Table 4). Four patients had small lesions with minimal discomfort, and did

Fig. 6.—This drawing shows a completed "far-and-near" suture.

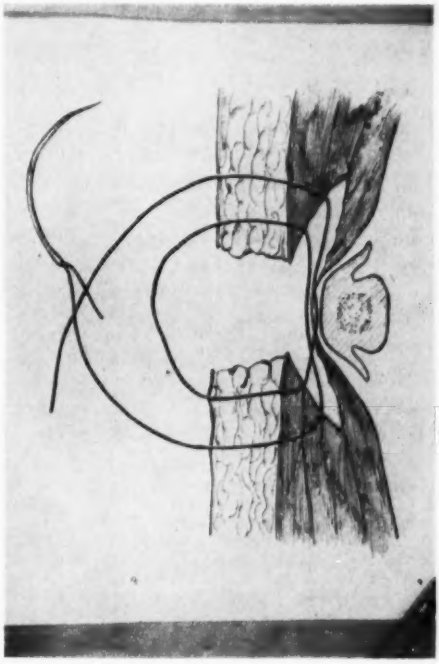


TABLE 2.—*Wound-Healing Complications Following Excision of Pilonidal Sinus with Primary Closure*

Complication		Treatment	Outcome	No. of Cases	Total Cases	Per Cent
Hematoma		Reopening of wound	Failure to heal	1		
			Satisfactory	5	6	4.8
Infection	(a) Major	Reopening of wound	Satisfactory	8		
	(b) Minor (seropurulent drainage from 1 or more sutures)	Conservative	Satisfactory	4	12	9.6
Slight skin separation	(a) Lower fourth of incision	Conservative	Satisfactory	5		
	(b) Center of incision	Conservative	Satisfactory	1		
	(c) Junction of midline incision & lateral extension	Conservative	Satisfactory	4	10	8.0

not wish further treatment. It is of interest that there were no recurrences in the 41 patients who had evidence of acute infection on admission (Table 5). It is probably significant that the majority of the recurrences were in patients who had had previous surgery. The recurrence rate was only 4.1% in the 73 patients who had never been operated upon before this admission. Finally, there were no significant postoperative complications other than those related to wound healing.

TABLE 3.—*Follow-Up Data on Primary Closure in Pilonidal Sinus: A Seven-Year Study*

Total patients	125
Patients followed	121 (96.8%)
Patients followed more than 1 ½ yr.	102
Economic disability	negligible
No symptoms	65%
Minimal tenderness	35%
Recurrent disease	13 (10.4%)

Comment

The postwar enthusiasm for excision and primary closure has waned, and marsupialization and various other techniques are now in the ascendancy. Nevertheless, before the various techniques of excision and primary closure are abandoned, adequate statistical evidence should be available to prove that the open methods of treatment are in fact superior. It is important, therefore, to continue to appraise and analyze the results of surgery for this vexing lesion and to keep accurate long-term records of the recurrences which take place. There is a natural aversion to a procedure such as the flap operation with primary closure. At first it strikes one as being a radical, somewhat bloody, somewhat too elaborate and formal a procedure to carry out in the treatment of what seems to be such a minor lesion. However, there is little or no discomfort following surgery, and the patient

TABLE 4.—*Recurrent Pilonidal Sinus: Results of Further Treatment*

Time of Recurrence	No. of Cases	Type of Operation	No.	Recurrence	Healed	Satisfied: Treatment Not Desired
0-6 mo.	7	Primary Closure	2	1	1	
		Marsupialization	3	1	2	
		None	2			2
7-12 mo.	4	Primary Closure	1		1	
		"Open Operation" *	2		2	
		None	1			1
13-18 mo.	2	Primary Closure	1		1	
		None	1			1

* Operations performed elsewhere.

TABLE 5.—*Recurrent Pilonidal Sinus Following Primary Closure Operation*
Relationship to Previous Attempts at Surgical Cure, Acute Infection, and Wound-Healing Complications

	No. of Operations	No. of Recurrences	Per Cent
No previous surgery	73	3	4.1
History of I & D only	21	2	9.5
History of surgery (all kinds)	52	10	19.2
History of definitive surgery (only)	31	8	25.8
All patients	125	13	10.4
Patients followed	121	13	10.7
Patients followed more than 1½ yr.	102	13	12.8
Acute infection on admission (preop. I & D in 15 pts.)	41	0	0
Patients with wound-healing complications	28	3	10.7

is ambulatory within a day or two after operation. After removal of the sutures on the eighth or ninth day the patient is discharged from the hospital, and there is in general no necessity for further medical care. The recurrence rate following this procedure is believed to be satisfactorily low as compared with the recurrence rate reported in the recent literature (Table 6). Even if it should be clearly proved that the recurrence rate following open methods of treatment, such as marsupialization, is appreciably lower, some consideration should still be given to the facts that with the primary-closure operation the period of postoperative morbidity is shorter, and there is no necessity for daily dressings, which require frequent visits to the hospital clinic or to the doctor's office. Many of the patients treated at this hospital have come long distances for treatment, some of them as far as 300 miles. Other patients live in relatively isolated rural districts, where skilled medical care is difficult to obtain. Proper postoperative care following any open operation would therefore require prolonged hospitalization.

Following excision and primary closure and prior to discharge from the hospital, it is important to give the patient careful instruction as to body hygiene. This is necessary in order to avoid ingrowing hairs or hair-follicle infection, which may be one of the important causes of recurrence in the primary-closure operation, as it is also thought to be following the various open operations. Meticulous skin closure and avoidance of overlapping of the wound are also important in this regard. However, failure completely to remove diseased tissue is believed to be the commonest cause of recurrence. In four of our patients with recurrences study of the excised specimen showed sinus tracts extending to the margin of the specimen. It was the opinion of the pathologist in these cases that the disease had been incompletely removed. In a fifth patient the wire stay sutures had been improperly removed, and retained wire fragments later eroded through the skin, resulting in further sinus tracts. In a sixth case there was failure to heal following a hematoma with subsequent evacuation. In a seventh case there was recurrence in a patient who had had a wound infection, followed by drainage and delayed healing of about 75 days. Postoperative wound infection has been infrequent and could be held down to lower figures if care were taken not to carry out primary closure in the presence of infection. As wound infections have generally been due to antibiotic-resistant organisms, it has become evident that systemic antibiotic therapy is of little value in the operative management of these patients. We have now discontinued the use of systemic antibiotics fol-

TABLE 6.—*Recurrence Rate as Reported in Literature*
Following Excision of Pilonidal Sinus by Various Methods and Followed for Varying Periods of Time

Type of Operation	Per Cent of Recurrence	References
Marsupialization	2 to 16%	1, 6, 7, 13
Open operation (all types)	3 to 33%	3, 6, 7, 9, 13
Primary closure (all types)	7 to 32%	3, 6, 9, 13
Primary closure (musculofascial flaps)	13 to 37%	4, 7, 13

TABLE 7.—*Wound Infection Following Excision of Pilonidal Sinus with Primary Closure*

	No. Pts. with Primary Closure	No. Wound Infections (Major & Minor)	
Total patients	125	12	9.6%
Acute infection on admission	41	9	21.9%
(I & D preop.)	(15)	(4)	(26.7)
No evidence of acute infection on admission	84	3	3.6%

Nine of the wound infections (75% of total) occurred in patients who had presented evidences of acute infection on admission.

lowing surgery for pilonidal sinus, but we have continued wound irrigation with an antibiotic solution. It might well be that irrigation of the wound with saline alone would be equally satisfactory. Four of the eight major wound infections, requiring reopening of the wound, have occurred within the last six months, and all of these were due to resistant staphylococci. Wound healing in the eight patients with major infection and in the six patients with hematoma took place in an average of six weeks. This is about the same period of time that is required for wound healing following either marsupialization or one of the techniques of partial closure. It was found in this study that, although patients who have acute infection on admission to the hospital can be operated upon, with a very low recurrence rate, the number of postoperative wound infections is apt to be high (Table 7). Considerable judgment obviously must be used in determining the time of surgery in such infected cases. In cases where the severity of the infection has required unroofing of the sinus tracts, or perhaps actual incision and drainage, it is probably advisable that definitive surgery be indefinitely postponed until evidence of recurrence and chronic disability become apparent. It is well known that some patients, following incision and drainage, have no further trouble from this disease, presumably because of destruction of the epithelial lining of the sinus by necrosis.

Summary and Conclusions

En bloc excision, mobilization of equal musculofascial flaps of gluteus maximus muscle, and primary closure by means of removable far-and-near sutures of stainless-steel wire has been carried out in 125 unselected patients with symptomatic pilonidal sinus. These patients were operated upon during a seven-year period of study by 12 different surgeons. Primary wound healing was obtained in 111 patients, or 88.8%. Of the 61 patients operated upon personally by either of us, there was primary wound healing in 60 patients, or 98.4%. Follow-up studies were carried out in 121 patients, or 96.8% of the total, and 102 patients have been followed for more than 18 months. There were 13 recurrences, in 10.7% of the patients followed, or in 10.4% of the total number. If technical errors could be avoided, it is believed that the recurrence rate could be held down to less than 5%. Recurrences were found to have been most frequent in patients who had previously had surgical treatment, and wound-healing complications were most frequent in patients who showed evidence of acute infection at the time of admission. In conclusion, our enthusiasm for the primary-closure technique of operative treatment of pilonidal sinus has continued to remain high. This operation in our experience has provided the patient with a thin, strong, nontender scar, with minimal deformity, and a protective pad of fat and fascia over the bony prominence of the coccyx and sacrum. It is a simple operative procedure, which is applicable to the treatment of all but the most extensive lesions. It can be carried out with low morbidity and with a reasonably low recurrence rate. Wound infection can be held down to a level acceptable for any clean operative procedure so long as satisfactory clinical judgment is exercised as to the time of surgery

and so long as the surgeon is careful to obtain complete hemostasis and a meticulous wound closure.

Veterans Administration Center.

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Spontaneous Rupture of the Normal Spleen

Review of the Literature and Report of One Case

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Up to 1957 there have been reported in the literature 40 cases of nontraumatic rupture of the normal spleen. The purpose of this paper is to report an additional case and to review the literature.

The causes of rupture of the spleen may be classified as follows:

1. Nontraumatic rupture of the normal spleen. This is uncommon. 2. Traumatic rupture of the normal spleen. This trauma may occur in (*a*) physiologic states, such as pregnancy, parturition, coitus, and straining at stool; (*b*) nonpenetrating injuries; (*c*) penetrating wounds, and (*d*) intra-abdominal trauma associated with catastrophic abdominal events, such as acute pancreatitis or a ruptured viscus. 3. Spontaneous rupture of a diseased spleen, as in leukemia, malaria, typhoid, portal thrombosis, Banti's disease, infectious mononucleosis, splenic infarct, puerperal sepsis, relapsing fever, pneumonia, and vascular disease of the spleen or its pedicle. 4. Traumatic rupture of a diseased spleen. This may occur with less severe insults than those in Group 2.

It is our purpose to comment only on the cases of nontraumatic rupture of the normal spleen. In 1946 Babson and Morgan [1] reviewed the literature on this subject and extracted 35 authenticated cases. They added two cases of their own, one of which is well documented, and the other occurred five days following surgery for perforated gastric ulcer. The latter case should be discounted, as it is well known that trauma to the spleen does occur in the course of gastric surgery. This is commonly caused by retraction. Thus, 36 cases of nontraumatic rupture of the normal spleen were reported prior to 1946. In 1952 Nicoll [2] reported a case of rupture of the spleen in a man who had had malaria 25 years previously and whose spleen ruptured after lifting a milk churn, which was part of his normal occupation. There was no evidence of malaria on examination of the spleen. Hamilton,[3] in 1953, added a report of one case with no history of trauma. In 1953 Volin and Billingsley [4] reviewed the controversy on whether nontraumatic rupture of the normal spleen occurs at all. They estimated that some 40 or more cases had been reported in the literature since the condition was first recognized, 80 years previously, and added one well-studied case. Kobak, Weiss, and Sturman,[5] in 1954, reported a case of spontaneous rupture of a normal spleen simulating ruptured ectopic pregnancy. In 1955 Byrd and Couch [6] reported a case of rupture of the spleen with associated pancreatitis. Other recent reports of rupture of the spleen with associated intra-abdominal pathology have appeared. Thompson [7] reported a case of rupture of the spleen associated with perforated gastric ulcer. Harbison, Patton, and Moyer,[8] in 1954, reported a case of rupture of a congenitally abnormal spleen in a case of situs inversus. In these three cases there was associated intra-abdominal pathology which acted as an insult to the spleen, and they cannot readily be included with the cases of nontraumatic rupture. In 1954 Madison, ReMine, and Chance [9] reported two cases of splenic bleeding, namely, one of bleeding from a branch of the splenic artery and one of subcapsular rupture. The second patient had cholelithiasis and a small

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aortic aneurysm just above the aortic bifurcation. This patient recalled having fallen on his left side prior to the rupture. These cases will not be included in the present review. Thus, since 1946 four additional case reports of nontraumatic rupture of the normal spleen have appeared, making a total of 40 cases. We are reporting the 41st case of nontraumatic rupture of the normal spleen.

Report of Case

A 50-year-old woman was admitted to the Bronx Hospital on March 20, 1955, with a history of 24 hours of diffuse abdominal pain, nausea, and vomiting. About noon on the day of admission the patient felt weak and complained of increasing abdominal pain, which radiated to both shoulders. The pain had reached its maximum intensity just prior to hospitalization, when she began to perspire profusely. There was no history of blood in the vomitus and no history of melena. The patient had had a normal bowel movement the day prior to admission. Her menses had been regular, and her next anticipated menstruation was due to occur within the next four to five days. There was no history of trauma. The past history revealed that the patient had been in good health prior to the onset of her present illness. She had had no serious illnesses and no major operations. She had borne two children, both of whom were living and well.

On admission the patient was in profound shock. Her pulse was weak and thready and at a rate of over 150 per minute. Blood pressure was not obtainable. She was stuporous and pallid. The abdomen was rigid and diffusely tender, with marked rebound tenderness. No masses could be palpated. Examination of the heart and lungs was negative. Rectal examination revealed bilateral tenderness to peritoneal tug. Stool was negative for blood. On vaginal examination there was diffuse pelvic tenderness.

Admission blood count was 3,310,000 red blood cells; 59% hemoglobin, and 19,600 white blood cells per cubic millimeter, with 87% neutrophils, 10% lymphocytes, and 3% monocytes. Urinalysis showed 2+ acetone. Serum amylase was 23 units (normal up to 110 units in our laboratory). X-ray films of the abdomen and chest were taken. Multiple calcific densities were present in the region of the gallbladder.

Our initial impression was that this patient was suffering from a retroperitoneal hemorrhage or from a ruptured ectopic pregnancy. Immediate measures were taken to correct the state of shock. Blood transfusion was started through a venous cut-down, and an intravenous infusion of norepinephrine was given. When the blood pressure was stabilized, the patient was taken to the operating room for an exploratory laparotomy. Operation was started with a blood pressure of 110/75. Initially, a right lower rectus-muscle-splitting incision was made. About 2 liters of blood was aspirated from the abdominal cavity. The pelvic organs were inspected and found to be normal. Clotted blood was found in the left gutter. The spleen was palpated and found to be markedly enlarged and the source of the hemorrhage. The lower abdominal wound was packed with moist pads, and left subcostal incision was made. Splenectomy was performed. Both wounds were then closed. The patient left the operating theater in fair condition, with a blood pressure of 90/65. During the first postoperative day blood transfusions and norepinephrine were continued. Twenty-four hours after surgery the blood pressure was stabilized, and norepinephrine and blood transfusions were discontinued. The patient received a total of 2,500 cc. of blood.

Postoperative Reevaluation of the Patient.—In view of the findings at surgery, careful and detailed questioning of the patient and her family, including the referring physician (a member of the immediate family), revealed no history of recent or remote trauma. The family did not own an automobile, and it was unusual for the patient to leave her duties at home as a housewife. Heterophil antibody studies and blood smears for Downey cells were negative on the first postoperative day.

On the fourth postoperative day the patient was out of bed and tolerating a soft diet well. On the eighth postoperative day the patient had an attack of dizziness, faintness, and speech difficulty. Although apparently understanding the spoken word, the patient was unable to express herself verbally. Neurological examination revealed a transient positive right Babinski and vocal motor aphasia. In two hours dizziness and faintness disappeared and the patient felt better.

Hematological consultation was made with Dr. Walter Solomon. Bleeding time was one minute; prothrombin time was 100% normal, and the platelet count was 920,000 per cubic millimeter, with some giant and misshapen forms. It was his impression that the patient had suffered a thrombosis of a small branch of the left middle cerebral artery, related to a postsplenectomy elevation of platelets. Anticoagulant therapy was started with heparin and bishydroxycoumarin U. S. P. (Dicumarol). In two days the motor aphasia disappeared completely. On the 11th postoperative day the patient was discharged from the hospital on a maintenance dosage of bishydroxycoumarin.

On pathological examination, the spleen was found to measure 13×13 cm. It was markedly congested and hemorrhagic throughout, and its capsule was missing in several areas. The cut surface was purplish, congested, and somewhat friable. Sections were taken for microscopic examination. These revealed areas of hemorrhagic necrosis. In some areas the sinusoids were dilated and contained little or no blood. Further sections were taken from several additional areas of the spleen, and these revealed no additional changes. The pathological diagnosis was rupture of the spleen.

Comment

Study of this case was made from the points of view of diagnosis, the possible pathological mechanisms involved in nontraumatic rupture of the spleen, and the hematological byproducts of surgery.

Helpful clinical findings in distinguishing rupture of the spleen from other acute abdominal emergencies are evidence of blood loss; localized pain and tenderness in the epigastrium, the left upper abdominal quadrant, and the left costovertebral angle; presence of an enlarged spleen; positive Kern's sign (pain referred to the left shoulder), and the Ballance sign (shifting dullness in the right flank and nonshifting dullness in the left flank). Most helpful in making a correct diagnosis is the x-ray, which may show dilatation of the stomach, serration of the margins of the greater curvature of the stomach, elevation of the left portion of the diaphragmatic dome, downward displacement of the splenic flexure of the colon, compression of the fundus of the stomach, separation of intestinal loops by fluid, obliteration of the splenic shadow, increased density of the shadow under the left diaphragmatic dome, displacement of the stomach to the right, or a progressively larger splenic shadow, revealed in some special cases by serial x-ray studies.[10] Among these x-ray signs, the displacement of the stomach and that of the splenic flexure of the colon, with progressive increasing density and size of the splenic shadow, are probably the most important.

In our patient the postoperative increase in platelets and subsequent cerebral intravascular occlusion were adequately controlled with anticoagulants. Follow-up studies of this patient after discharge from the hospital have revealed a gradual return to normal platelet level.

Spontaneous rupture of a normal spleen occurs in the absence of any clinically recognizable trauma or precipitating incident. What are the possible explanations for the occurrence of this catastrophe?

1. Nonrecognized trauma in the patient's normal activities, i. e., minor physical injuries

2. Unrecognized physiologic insults, causing changes in vascular dynamics, as when intra-abdominal pressure is increased as the result of lifting, straining, or bending

3. Insults to the homeostasis from associated pathology, such as cholelithiasis or chronic pancreatitis

4. Long delay between the time of a subcapsular rupture and free intraperitoneal rupture of the spleen, so that the patient forgets the trauma

5. Localized unrecognized focal splenic pathology destroyed by the hemorrhage or hematoma, such as a cyst or hemangioma. In our case there was associated asymptomatic cholelithiasis.

Summary

A case of spontaneous rupture of a normal spleen is documented as the 41st case to be reported in the literature. A classification of causes of splenic rupture is presented. Possible mechanisms responsible for the phenomenon of spontaneous rupture of the normal spleen are discussed.

2021 Grand Concourse (53).

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Cardiac Myxoma

Surgical Treatment in Four Cases

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Primary tumors of the heart, although rare, are being recognized more frequently as a result of increasing interest in cardiovascular surgery and improvement in diagnostic techniques. Intracardiac myxomata comprise some 50% of primary cardiac tumors and are located in the left atrium in approximately 75% of cases. Myxomata occur in persons of all ages, including the newborn, but the majority of patients are between 30 and 60 years of age. The lesion occurs in females three times as frequently as in males. Although the majority of these lesions arise at the fossa ovalis, in some cases the point of attachment is the valve of the inferior vena cava and the left ventricle.

Tumors of the heart drew the attention of pathologists as early as the 17th century, as evidenced by the writings of Malpighi, in 1666, in "De polypo cordis dissertatio," and many others, quoted at length in the monograph published by Mahaim [15] in 1946. Controversy regarding the true nature of cardiac myxoma has revolved around the question of whether they were neoplastic or simple intracardiac thromboses. Thorel [25] led the arguments for the thrombotic theory, stating that these patients suffered from circulatory deficiency and thrombosis in other parts of the body. Actually, he based his conclusions on histologic descriptions from the literature without seeing any of these tumors himself. Ribbert [20] refuted this theory and considered the myxoma a true neoplasm. As already stated, myxomata are usually found in the atria and are attached to the interatrial septum, whereas thrombi occur in diseased hearts and are located with equal frequency in the atria and in the ventricles, especially in the auricular appendages. Myxomata are much larger and less cellular than thrombi and lack the stratification characteristic of thrombi. Hemosiderin and many capillaries are present in myxomata, but these findings are presumably due to the stress placed upon the tumor by the blood stream. If one accepts the theory of neoplastic basis for these lesions, the origin of the tumor must be explained. Ribbert [20] believed the lesion originated from myxoid tissue in the embryonic endocardium. Prichard [18] could not demonstrate myxomatous tissue around the fossa ovalis but demonstrated that subendocardial tissue in this region was thicker and denser than in any other parts of the heart and correlated this with the connective tissue origin of the tumor. Stout [24] considers the myxoma a true benign neoplasm made up of well-differentiated cells, stellate in shape, having fine protoplasmic processes and separated by a loose mucoid stroma with intermingled reticulin fibers. It was suggested by Stout that the intercellular mucoid substance consisted of hyaluronic acid rather than mucus, since it was liquefied by hyaluronidase.

Symptoms and clinical findings produced by intracardiac myxomata depend upon location of the tumor. In myxoma of the left atrium the clinical picture closely re-

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sembles mitral stenosis. Indeed, most of these lesions recognized clinically in the past 10 years have been discovered at mitral exploration for mitral stenosis. The mitral murmur tends to be variable and varies with change in position and posture. The mitral diastolic murmur is heard with the patient in the sitting or standing position and may be replaced by a systolic murmur when the patient is lying down. Dyspnea, which is intermittent at first, becomes progressive. Attacks of cyanosis and paroxysmal dyspnea occur on lying down, owing to pulmonary congestion. Blood pressure, especially pulse pressure, is low, secondary to the obstructive process. Sudden occlusion or obturation of the mitral orifice, usually produced by leaning forward, leads to syncope and occasional epileptiform attacks, due to cerebral anoxia. Congestive heart failure, which is sudden and refractory to digitalis and diuretics, may occur, and arrhythmias, such as auricular tachycardia and fibrillation, also occur.

Myxoma of the right atrium may simulate tricuspid stenosis, constrictive pericarditis, or superior vena caval syndrome. Absence of a paradoxical pulse may aid in differentiating this lesion from constrictive pericarditis. Peripheral edema, ascites, and pleural effusions are common in advanced stages of the lesion as venous pressure increases.

Ultimately, embolic phenomena appear as fragments of tumor, or attached thrombi break off the surface of the tumor. Recurrent peripheral emboli occurring in the absence of auricular fibrillation should suggest the possibility of a myxoma. Microscopic examination of the embolus after removal from the artery may suggest the presence of the myxoma. Embolism to the extremities, viscera, brain, and coronary arteries may result from left atrial myxoma, whereas pulmonary embolism is common with right atrial lesions. The clinical picture may be suggestive of subacute bacterial endocarditis, but splenomegaly is absent and blood cultures are negative.

Diagnosis may be established by either angiocardiography or cardiac catheterization. A large space-occupying globular lesion in the atrium demonstrated in the angiocardiogram is almost certain proof of a myxoma. Right-heart catheterization may

TABLE 1.—*Results of Operation in Atrial Myxoma According to Method Used (Collected Series)*

Author	Year	Location of Tumor	Result
A. Closed technique			
1 Goldberg et al.[10]	1951	Left atrium	Died; incomplete excision; cardiac arrest
2 Steinberg, Dotter, and Glenn[23]	1953	Left atrium	Died
3 Bahnson[1]	1953	Right atrium	Partial excision; died in 24 hr.; gastric dilatation
4 Bahnson[1]	1953	Left atrium	Died; dislodgment tumor; blockage left ventricle
5 Cooley	1953	Right atrium	Died; pulmonary embolus
6 Likoff et al.[14]	1954	Left atrium	Died; fracture of tumor; occlusion midthoracic aorta
7 Nichols[16]		Left atrium	Died
8 Nichols[16]		Left atrium	Died
9 Nichols[16]		Left atrium	Died
10 Nichols[16]	1955	Left atrium	Survived partial excision
11 Paquet[17]	1956	Right atrium	Died
12 Paquet[17]	1956	Left atrium	Died; ventricular fibrillation
13 Paquet[17]	1956	Left atrium	Died
14 Fell[9]		Right atrium	Died
15 Fatti[8]	1957	Right atrium	Survived
B. Open technique Hypothermia			
16 Bigelow et al.[2]	1955	Left atrium	Survived
17 Scannell and Grillo[22]	1955	Left atrium	Survived; ventricular fibrillation
18 Brock[3]	1956	Left atrium	Died; ventricular fibrillation
19 Robertson[21]	1956	Left atrium	Survived
20 Chin and Ross[6]	1957	Left atrium	Survived; ventricular fibrillation
21 Hopkins[13] Cardiopulmonary bypass	1957	Right atrium	Survived
22 Clowes et al.[5]	1954	Left atrium	Died; tumor excised
23 Crafoord[7]	1954	Left atrium	Survived
24 Bahnson[1]	1956	Left atrium	Survived
25 Hanlon[11]	1957	Right atrium	Survived
26 Coates and Drake[4]	1957	Right atrium	Survived
27 Lyons et al.[15]	1957	Right atrium	Survived
28 Cooley	1957	Left atrium	Survived
29 Cooley	1957	Left atrium	Survived
30 Cooley	1958	Right atrium	Survived

TABLE 2.—*Clinical Experience with Cardiac Myxoma*

Case	Age	Sex	Location of Tumor	Date of Operation	Technique	Result
1	43	F	Right atrium	12/18/53	Closed; bimanual extraction	Died; pulmonary embolism tumor fragments
2	50	M	Left atrium	6/25/57	Open; cardiopulmonary bypass	Excellent
3	49	F	Left atrium	9/25/57	Open; cardiopulmonary bypass	Excellent
4	48	F	Right atrium	3/20/58	Open; cardiopulmonary bypass	Excellent

definitely establish the presence of a myxoma of the right atrium. The circuitous course of the catheter as it encounters the obstructing tumor is strongly suggestive of the diagnosis, and the presence of low normal pressures in the right ventricle and pulmonary artery with elevated right atrial and superior vena caval pressures is confirmatory. Catheterization findings in left atrial myxoma resemble those of mitral stenosis with increased pulmonary arterial and pulmonary capillary pressure.

Surgical treatment of these lesions has been successful in relatively few patients (Table 1). With development of techniques of open-heart surgery for a variety of cardiovascular lesions, the successful removal of myxoma was an almost inevitable step forward in expanding cardiac surgery. During the past five years four patients have been operated upon in our clinic for removal of intracardiac myxoma (Table 2).

Clinical Material

CASE 1.—A 43-year-old woman was admitted to Methodist Hospital Dec. 13, 1953, complaining of progressive exertional dyspnea. On physical examination the blood pressure was 100/80 mm. Hg, and no murmurs were audible over the heart. Venous pressure was elevated, and the liver was palpable 3 cm. below the costal margin.

Roentgenograms of the chest revealed right atrial and right venticular enlargement with inconspicuous pulmonary arteries. Electrocardiograms showed right-axis deviation and low amplitude in all leads.

The findings on cardiac catheterization follow.

	Pressure, Mm. Hg	Oxygen Content, Vol. %
Superior vena cava	18/7 (15)	7.2
Right atrium	19/7 (15)	6.9
Right ventricle	10/0 (4)	6.8
Pulmonary artery	15/5 (5)	7.0
Femoral artery	110/75 ..	...

The diagnosis of possible constrictive pericarditis was made, and thoracotomy was performed Dec. 18, 1953. A large myxoma was discovered, which filled the right atrium and extended into the right ventricle. With one index finger introduced inside the atrium, an attempt was made to deliver the tumor through a secondary incision in the atrial wall. As the tumor was being withdrawn from the heart, cardiac arrest occurred and resuscitative attempts were unsuccessful.

Autopsy revealed a massive myxoma attached to the fossa ovalis (Fig. 1). Death had presumably been due to embolism of tumor fragments into the pulmonary arteries.

CASE 2.—A 50-year-old white man complained of exertional dyspnea, not associated with orthopnea, cyanosis, substernal pain, palpitations, or loss of consciousness. At another hospital exploration of the mitral valve for mitral stenosis revealed a tumor mass in the left auricle attached to the interatrial septum. No attempt was made to remove the tumor. The auricular appendage was closed, and later he was referred to Methodist Hospital, on June 12, 1957.

Fig. 1 (Case 1).—Photograph of heart at autopsy, showing friable tumor mass attached to atrial septum and protruding through tricuspid valve. Death resulted from tumor embolism to lungs.

On physical examination the blood pressure was 90/60 mm. Hg., with a small pulse of 80 per minute. The neck veins were not congested. There were splitting of the second sound and a Grade 2 diastolic murmur in the mitral area. The pulmonic second sound was equal to the aortic second sound.

Circulation time (arm-to-tongue) with dehydrocholic acid U. S. P. (Decholin), 40 seconds. The electrocardiogram showed P-waves, suggestive of left atrial enlargement, and clockwise rotation of the heart, with a pattern suggestive of right ventricular hypertrophy and digitalis effect. Roentgenograms of the chest (Fig. 2) showed slight cardiac enlargement with prominence of the undivided portion of the pulmonary artery.

On June 25, bilateral anterior thoracotomy was performed, with entrance in the fourth intercostal spaces. Cannulations for cardiopulmonary bypass were performed, as shown in Figure 3, and 1.5 mg. of heparin per kilogram of body weight was administered. With the pump oxygenator functioning, the left atrium was opened widely, revealing a gelatinous, globular, pedunculated tumor mass, measuring 5 cm. in diameter, attached to the interatrial septum. The lesion was completely removed, and the atriotomy was repaired. The group oxygenator was used for only eight minutes. The patient recovered from operation and was entirely symptom-free one year after operation.

CASE 3.—A 49-year-old woman was admitted to St. Luke's Hospital on Sept. 16, 1957, with a tentative diagnosis of mitral stenosis. She had moderate exertional dyspnea with feelings of faintness on stooping or leaning forward. Variable mitral systolic and diastolic murmurs were audible, with an increase in the pulmonic second sound.

Roentgenograms of the chest revealed the so-called mitralized contour. Cardiac catheterization was performed, revealing the following findings:

	Pressure, Mm. Hg.	Oxygen Saturation
Superior vena cava	..	74
Right atrium	4	77
Right ventricle	60/5	75
Pulmonary artery	45/25	78
Pulmonary wedge	20 mean	..

On Sept. 25, 1957, a left anterior thoracotomy was performed through the left fourth intercostal space in order to explore the mitral valve through the left auricular appendage. At exploration a large polypoid mass attached to the atrial septum was discovered. The appendage and thoracotomy were closed temporarily, and the patient remained in the recovery room for the next four hours while the pump oxygenator was prepared and heparinized blood was drawn from donors.

The incision was reopened, and cannulations were performed for bypass (Fig. 3). With the extracorporeal circuit providing cardiopulmonary bypass, the left atrium was opened widely and the tumor was completely excised. A full thickness of atrial septum was removed, and the defect was repaired with silk sutures, after which the atriotomy was repaired. A mild coronary air

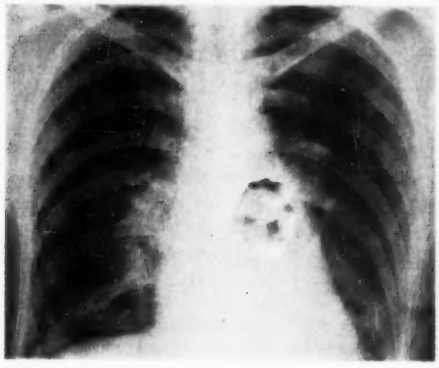


Fig. 2 (Case 2).—Roentgenogram of chest, showing mitralized cardiac contour. Superimposed myxoma removed from left atrium shows relative size of lesion as compared with heart.

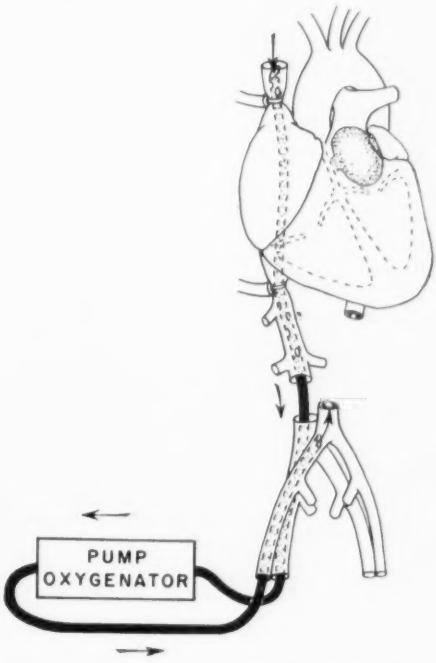
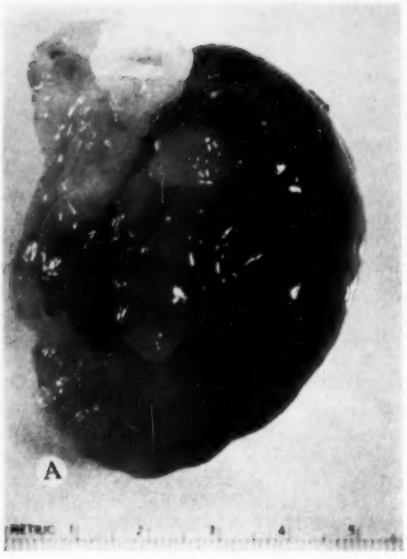


Fig. 3.—Drawing showing method of cardiopulmonary bypass used in Cases 2 and 3. Venae cavae were cannulated with a single catheter passed through the right common femoral vein. Oxygenated blood was returned by the femoral artery.



resulted in cyanosis and extreme anxiety. Physical examination revealed a thin, chronically ill woman, who was orthopneic and very dyspneic, even at rest. The neck veins were greatly distended (Fig. 5), and venous pressure was 300 mm. saline. The cheeks were flushed, and circumoral cyanosis was evident. Blood pressure was 90/75 mm. Hg. No cardiac murmurs were present. Physical findings of bilateral pleural effusion with ascites were evident, and a 2+ ankle-pitting edema was noted. The liver was moderately enlarged and tender.

Roentgenograms of the chest showed moderate cardiac enlargement with pulmonary congestion and bilateral pleural effusion (Fig. 6). The electrocardiogram suggested right atrial enlargement and extremely low voltage of all cardiac complexes.

The findings on cardiac catheterization were as follows:

	Pressure, Mm. Hg	Oxygen Content, Vol. %
Superior vena cava	22 (mean)	...
Right atrium	22 (mean)	8.3
Right ventricle	15/5	8.7
Pulmonary artery	15/9	8.7
Cardiac index	1.24 liters	...

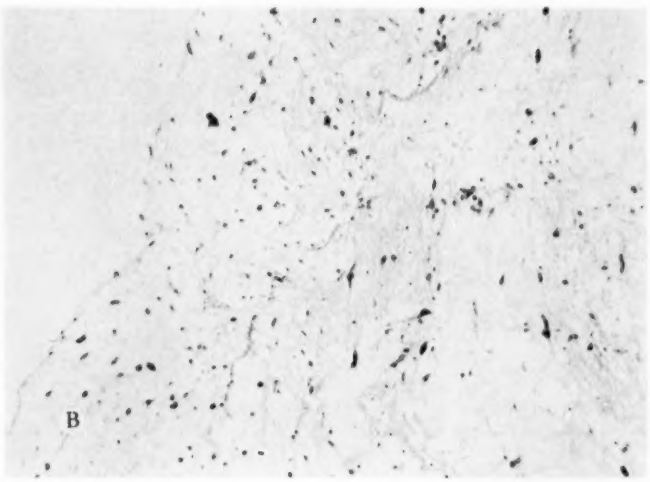


Fig. 4 (Case 3).—*A*, photograph of specimen of myxoma of left atrium removed, showing full thickness of atrial septum removed with tumor pedicle. *B*, photomicrograph of specimen, showing smooth endothelial surface, stellate cells, and loose myxomatous stroma.

embolism occurred, which cleared on continued perfusion with the pump oxygenator.

Her recovery after operation was satisfactory, and she was dismissed from the hospital 18 days later. The tumor consisted of loose, pale-stained substance in which numerous stellate cells were present (Fig. 4). The surface of the tumor was covered by a single layer of cells.

Case 4.—A 48-year-old white woman was admitted to Methodist Hospital on March 13, 1958, with ankle edema and progressive weakness and shortness of breath of one year's duration. Dyspnea had become so severe that the slightest exertion

The catheter entered the right atrium with difficulty and followed a circuitous course in reaching the right ventricle. The diagnosis of myxoma of the right atrium was made, and operation was performed on March 20, 1958.

A bilateral anterior fourth intercostal space incision was made and a large volume of pleural and pericardial fluid was released. The right atrium was completely filled with a tumor mass, which interfered with the usual type of can-

Figure 5

Fig. 5 (Case 4).—Photograph of patient, showing extreme distention of neck veins produced by large right atrial myxoma.

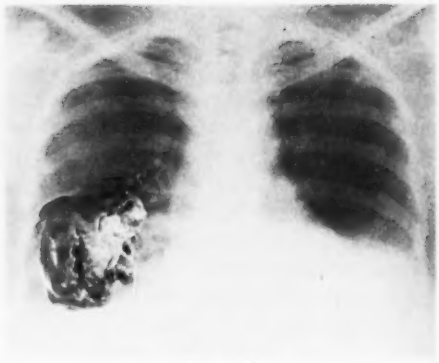


Figure 6

Fig. 6 (Case 4).—Roentgenogram of chest, showing moderate cardiac enlargement and bilateral pleural effusion. Specimen superimposed on the film explains the severe degree of the tricuspid obliteration produced by the tumor.

mulation used for cardiopulmonary bypass. The method finally used is illustrated in Figure 7. Bypass was started, and the right atrium was incised widely. The tumor was delivered, and its broad attachment at the fossa ovalis was separated and the atriotomy was repaired. The duration of bypass was nine minutes.

Her recovery from operation was gradual, and she was dismissed from the hospital one month later. Examination six months later revealed a striking recovery, with almost complete relief of symptoms. Electrocardiograms showed return of normal amplitude of the complexes and sinus rhythm.

Comment

Prior to development of methods of open-heart surgery, results of attempted surgical removal of atrial myxoma were poor. In fact, only 2 patients among 15 survived, and in only 1 of these was the lesion completely excised (Table 1). This single successful result, reported by Fatti,[8] was accomplished by a unique bimanual method, using one index finger in the left atrium and the other in the left ventricle, inserted through separate cardiotomies. The tumor pedicle was detached from the atrial septum by fingernail dissection. In spite of this successful case, one must conclude that closed methods of surgical removal are unsatisfactory.

Hypothermia as a means of obtaining open-heart conditions for removal of intracardiac myxomata has been reported in six cases (Table 1). It was appropriate that Bigelow,[2] who is a pioneer in hypothermic techniques, should have been the first to apply this technique successfully to a cardiac myxoma. The limitations of this method of open-heart surgery, including particularly the high incidence of arrhythmias, are now well known, and this is apparent from the fact that one-half of patients operated upon

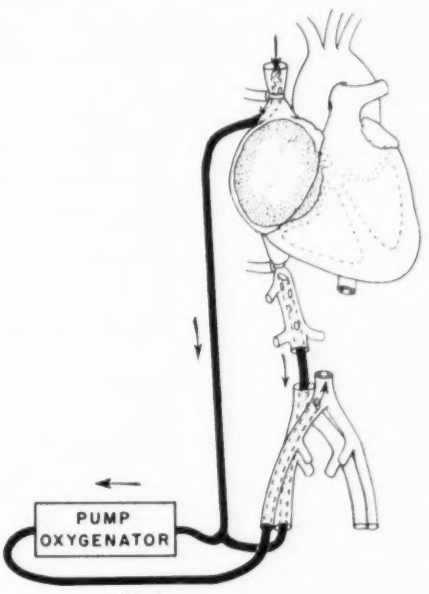


Fig. 7 (Case 4).—Drawing showing method of cannulation. Catheterization of cavae was performed individually because of the massive size of the lesion.

by this method developed ventricular fibrillation.

Crafoord first successfully used temporary cardiopulmonary bypass with a pump oxygenator in removing a left atrial myxoma. Including his case and the three cases reported herein, a total of eight successful operations of this type have been reported, and undoubtedly others have already been successfully done. This method provides optimum conditions of exposure and operating time to permit total excision of this lesion. If the atrial septum must be sacrificed with the tumor pedicle, repair of the septum may be performed with sutures. Loose fragments of tumor should be carefully removed from the cardiac chambers to prevent embolism.

Summary

The commonest intracardiac tumor is the myxoma, which is a benign, slowly growing tumor, usually attached to the atrial septum. Symptoms are predominantly caused by obstruction of the mitral or tricuspid valves or by embolism from the tumor surface. The true pathologic nature of the lesion is not completely established, but evidence strongly supports a neoplastic origin.

Surgical removal of myxoma has been firmly established with development of techniques for temporary cardiopulmonary bypass. Four cases of intracardiac myxoma are reported, and in three of these bypass was successfully used in removal of the tumor.

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Venoarterial Pumping for Relief of Intractable Cardiac Failure in Man

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The use of mechanical substitutes for the heart to pump blood from the great veins to the aorta in congestive failure has been proposed,[1,2] and a heart-lung machine has been used in the support of patients with myocardial infarction.[3] Experimental work suggests that acute heart failure in animals may be relieved by venoarterial pumping without an oxygenator.[4] Our own animal studies[5] have shown that it is possible to pump about half the systemic venous return into the lower aorta without significant impairment of the oxygen supply to the vital organs. In normal animals the cardiac output is reduced by this procedure, and there may be an increase in the total systemic blood flow. Venoarterial pumping has been maintained for as long as 53 hours in a dog without serious effects and with subsequent survival.

The present paper reports our experience with the first human case.

Report of a Case

The patient was a man aged 52 with a history of recent abdominal pain and swelling. Two weeks before the procedure he was admitted to the hospital with moderate peripheral edema, ascites, and an elevated venous pressure. The electrocardiogram showed atrial fibrillation and right bundle-branch block. The blood pressure was 110/60 mm. Hg, and there was evidence of peripheral vasoconstriction. The patient was drowsy and confused. Treatment with mercurials and ammonium chloride produced diuresis at first, but quickly became ineffective. A water load did not increase the urine output. The serum Na was 115 mEq/L., Cl 85 mEq/L., and K 6.7 mEq/L.

A diagnosis of constrictive pericarditis or cardiac myopathy was considered. The low urine volume was attributed to a reduced cardiac output, and venoarterial pumping was performed in an attempt to increase systemic perfusion and produce a diuresis.

Preparation for Venoarterial Pumping.—The procedure was performed in the operating room under sterile precautions, using local procaine anesthesia with the patient under light sedation with intravenous meperidine (Demerol). Heparin, 100 mg., was given intravenously, and clotting times were maintained above 30 minutes during the procedure by a slow infusion of heparin solution (1 mg/ml.). Recording and sampling polyethylene catheters were placed in the aortic arch through the left brachial artery, in the lower inferior vena cava through the right greater saphenous vein, and in the left innominate vein through the left external jugular vein.

Venous blood was recovered by gravity drainage through a No. 18 Bardic cannula inserted in the superior vena cava through the right external jugular vein, and returned to the terminal aorta through a similar cannula introduced through the proximal end of the interrupted right deep femoral artery (arteria profunda femoris). A Y-shaped connection allowed the insertion of a No. 12 Bardic cannula in the distal end of this vessel to perfuse the leg beyond the obstructed common femoral artery (Fig. 1).

The apparatus for venoarterial pumping consists of a collecting chamber and two pumps.[6] A thin-walled, transparent Silastic collecting chamber of 200 ml. capacity is enclosed in a Plexiglas case suspended from a gram scale. The pumps are thick-walled Silastic chambers with Hufnagel-type ball valves at each end, enclosed in Plexiglas cases and driven by graded pulses of compressed air. The collecting chamber and the two pumps mounted in parallel are connected by Tygon tubing (⅜ in., inner diameter) and nylon adapters. The apparatus is as-

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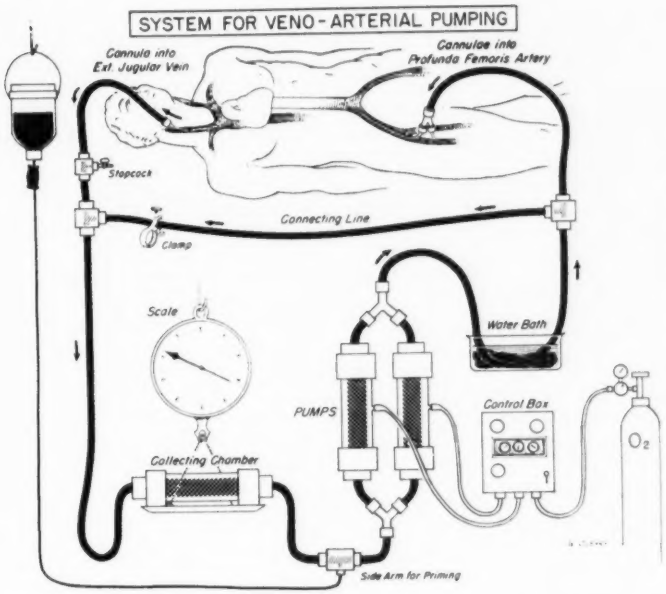

Fig. 1.—Apparatus for venoarterial pumping in man. Blood drains into the collecting chamber through a catheter in the external jugular vein and is pumped through the water bath into the lower aorta via the deep femoral artery. A small catheter in the distal end of the artery perfuses the leg. The stopcocks and connecting line used in priming and the removal of air are also shown.

sembled and autoclaved as a single unit. After connecting the venous and arterial cannula, the extracorporeal system is primed with 800 ml. of compatible citrated bank blood and cleared of air by aspiration from a side-arm while pumping through a connection between the arterial and the venous lines (Fig. 1).

Operation of the System.—Perfusion is begun by unclamping the cannulae and starting the pump with the connecting line occluded. The collecting chamber is distended at priming to the limits allowed by the Plexiglas case. When blood is pumped into the patient at a rate less than the maximum possible venous drainage, the collecting chamber remains distended, and the system will operate for a long period without adjustment. The volume of blood in the extracorporeal system is rigidly controlled. Excessive loss from the great veins is prevented by the limited capacity of the collecting chamber; and if venous drainage is obstructed, this chamber collapses and the patient receives less than 200 ml. of additional blood. The time taken for the pump to remove a 100 gm. of blood from the collecting chamber when the venous drainage is temporarily occluded is used as a measurement of the extracorporeal flow.

Blood is drawn from the collecting chamber into the pumps during their relaxation phase and passes to the terminal aorta. The arterial line passes through a water bath, allowing control of the patient's body temperature.

Course of the Procedure.—Venoarterial pumping was begun at a rate of 700 ml/min. but was soon increased to 1 L/min. The mean venous pressure was 30 mm. Hg when first measured, but fell to 12 mm. Hg while the apparatus was being prepared. During the first 16 hours of perfusion the venous

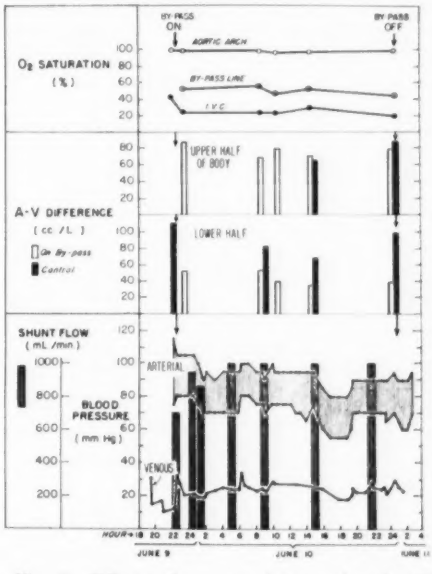

Fig. 2.—Effects of venoarterial pumping for 26 hours in man.

pressure was between 20 and 28 mm. Hg, and the systemic blood pressure remained above 90/70 mm. Hg (Fig. 2). Body temperature was kept constant, and the signs of peripheral vasoconstriction quickly disappeared. The heart rate remained unchanged.

The oxygen saturation of blood in the extracorporeal line remained similar to that in the superior vena cava throughout the procedure (43% to 56%). The inferior vena caval saturation fell from 43% initially to from 18% to 29% during perfusion. The arteriovenous oxygen difference in the part of the body draining to the superior vena cava was unaffected by pumping. Assuming that the lower limbs were supplied entirely by blood from the shunt line, the arteriovenous oxygen difference in this region fell to approximately half the control value during the procedure (Fig. 2). There was no change in buffer-base or blood urea. The arterial pCO_2 remained low throughout, as the patient was moderately dyspneic.

During the first 12 hours of perfusion the urine output was 25 ml/hr. A load of 800 ml. isotonic saline was then given and was followed by a slight rise in urine output to 40 ml/hr. for the next four hours. The serum Na did not change significantly.

From the 16th to the 21st hour there was a fall in blood pressure to 80/55 and of mean venous pressure to 18 mm. Hg (Fig. 2). In view of the slight response to previous fluid load and continuing blood loss from the operative sites, 1 liter of isotonic saline and 3 units of blood were given in the next four hours. The blood pressure rose to 90/70 and the venous pressure to about 25 mm. Hg, but there was no diuresis. Venoarterial pumping was therefore discontinued after 26 hours.

Effect of Venoarterial Pumping on Blood Elements and Chemistry

Duration of Perfusion, Hr.	Control	1	10	16	26
Hematocrit, %	48	48	42	40	41
Fibrinogen, mg. %	--	495	465	430	440
Platelets, per cu. mm.	--	153,000	111,000	80,000	74,000
Na, mEq/L.	115	113	114	116	121
K, mEq/L.	6.7	7.2	7.0	7.2	7.2
Cl, mEq/L.	85	--	88	89	95
Buffer base, mEq/L.	42	41	41	41	42
Arterial pCO_2, mm. Hg.	26	25	27	25	19
Plasma hemoglobin, mg. %	--	--	5	5	--

During the procedure the hematocrit fell from 48% to 40%. The plasma hemoglobin was only 5 mg. % at the 10th and the 16th hours, and the plasma was clear in all the blood samples. The plasma fibrinogen was little affected, but the platelet count fell to 74,000 per cubic millimeter at the end of perfusion (Table). One hundred milligrams of protamine sulfate corrected the clotting time to 20 minutes when the cannulae were removed, and there was no undue hemorrhage after termination of bypass.

The patient's general condition was unchanged by the procedure, though the amount of peripheral edema had increased. Signs of vasoconstriction returned, and attempts to sustain the blood pressure with hypertensive drugs were unsuccessful. He died 48 hours after the end of the procedure. Autopsy showed hemochromatosis involving the liver, myocardium, and kidney. There was no indication of injury attributable to the procedure.

Comment

The apparatus used here has many advantages for prolonged venoarterial pumping. A completely closed system eliminates the possibility of air embolism and the deposition of blood products at blood-air interfaces,[7] while reducing the likelihood of infection. The small, rigidly controlled volume of the extracorporeal circuit makes for easy priming and prevents any serious changes in the patient's blood volume. The independence of electrical power eliminates a possible hazard to prolonged pumping. The system is simple, mobile, and inexpensive. The tubing is disposable, and the apparatus is easily cleaned and sterilized by autoclaving.

Disturbance of the formed elements of the blood is minimal with this apparatus, an essential prerequisite for prolonged pumping. The oxygen supply to the vital organs is not seriously affected with the flow used here,[5] and there is no change in electrolyte pattern as a result of the procedure.

The effects of venoarterial pumping in this patient were disappointing. The fall in arteriovenous oxygen difference for the lower limbs suggests that the pumped blood was, at least in part, diverted to areas of low vascular resistance. An increase in perfusion of the lower extremities would not

be expected to benefit the vital organs. A greater venoarterial flow may be more effective.

Conclusion

A system for venoarterial pumping without oxygenation previously tested in animals has been used for 26 hours in man. Though the patient's condition was not improved, harmful effects from the apparatus were not apparent during the procedure or at postmortem examination. Except for platelet depression, no serious damage to the formed elements of the blood or the coagulation mechanism was found.

The feasibility of prolonged venoarterial pumping in man has been demonstrated. More effective changes in systemic perfusion may result from larger venoarterial flows. The development of an oxygenator suitable for prolonged use would increase the scope of the procedure, and this aspect is at present being investigated.

Summary

The use of venoarterial pumping without an oxygenator in the treatment of intractable cardiac failure in man is described. Venous blood was pumped into the lower aorta at the rate of 1 L/min. for 26 hours without harmful effect.

Dr. Louis A. Selverstone and Dr. Harold Rhinelander permitted us to report this case, and Dr. H. Edward McMahon, of the Department of Pathology, New England Center Hospital, furnished the autopsy data.

The Glover Clinic, 269 S. 19th St. (3).

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External Laryngocele

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Laryngocele is a rare and interesting swelling of the neck. It is almost never mentioned in the differential diagnosis of cervical masses. The diagnosis is relatively simple if the entity is kept in mind.

Between the true and the false vocal cords is an elliptical, horizontal space, called the ventricle of Morgagni. Anteriorly, from the roof of the ventricle, arises an outpouching called the sacculus, or appendix. This structure may be only a shallow pouch or may extend as a long narrow prolongation as high as the superior edge of the thyroid cartilage, or even the hyoid bone (Fig. 1). In this latter situation, the sphincteric action of the thyroarytenoid muscles is lacking,[6] and during any action which produces repeated elevation of intralaryngeal pressure (chronic coughing, straining, wind-instrument playing, etc.) the pressure is transmitted to the sacculus, which may dilate to form a laryngocele.

As the sacculus dilates, it is usually retained by the thyrohyoid membrane, and the laryngocele presents internally within the larynx above the false vocal cord (ventricular band). Occasionally, if the dilating sacculus penetrates the thyrohyoid membrane, the laryngocele presents externally in the lateral neck through the upper portion of the anterior triangle (Fig. 1). Very rarely, a combined internal-external laryngocele occurs.[8]

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A few instances of bilateral laryngocele have been reported.[1,10] Virchow is given credit for the first accurate description of this entity, in 1867,[9] and since then approximately 80 to 90 cases have been reported; about 70% are of the internal, 25% of the external, and 5% of the combined, variety.

Internal laryngocele may cause hoarseness and/or obstructive dyspnea, but the external type is usually asymptomatic. The external cyst does often fluctuate in size, and it usually will collapse under external pressure, with a hissing noise and refill during forced expiration. Roentgenograms will show the gas-filled cyst (Fig. 2*A* and *B*) and are so pathognomonic that they should be ordered in the evaluation of every cervical mass.

The pressure from a laryngocele may interfere with lymph drainage enough to produce edema of the cords and larynx, as in our case. If the sac becomes infected, a pyelocele results.[2-4] If the sac ruptures, emphysema of the tissues of the neck will follow. Occasionally, carcinoma of the

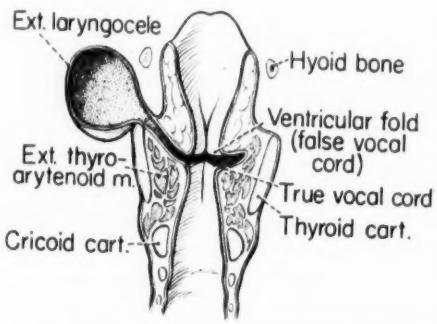

Fig. 1.—Frontal section of the larynx and external laryngocele. The laryngocele originates from the sacculus of the ventricle and passes superiorly beyond the thyroarytenoid muscle and through the thyrohyoid membrane into the lateral neck, where it forms an air-filled cyst.

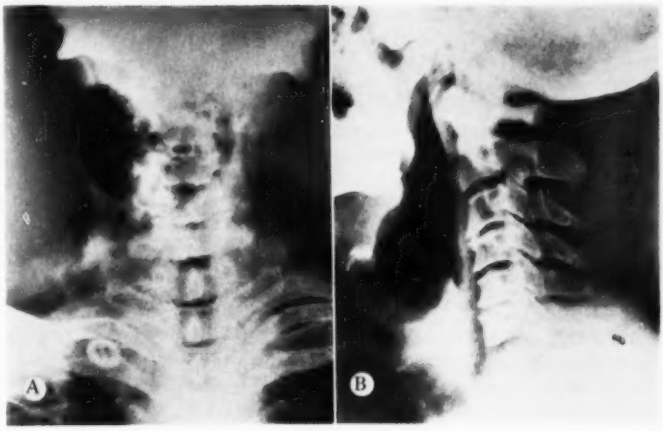

Fig. 2.—*A*, anteroposterior and, *B*, lateral roentgenograms of the neck, showing the air-filled laryngocele.

larynx is associated with laryngocele,[5-7] perhaps by coincidence.

Internal laryngoceles are removed via the endoscope or by thyrotomy. External laryngoceles are approached through the lateral neck and are amputated at the thyrohyoid membrane; the defect in this membrane should be repaired.

Report of a Case

A 48-year-old white man, a mechanic, was admitted to Mercy Hospital, Chicago, on Feb. 11, 1958, because of a progressively enlarging swelling in the right side of his neck. It had been present for five months and was said to fluctuate considerably in size. At first it had been asymptomatic, but during the preceding month the patient had become hoarse and moderately dyspneic.

Physical examination was normal except for the mass in the right side of the neck. It was situated over the anterior triangle near the mandible and measured 6×4×4 cm. It felt cystic but did not reduce in size with pressure. It was nonpulsatile and apparently moved upward a little with deglutition. There was no redness, tenderness, or edema.

Direct laryngoscopic examination revealed a swollen epiglottis, displaced to the left; neither vocal cord could be visualized adequately because of edema of the ventricular bands. Because laryngeal carcinoma could not be excluded, a biopsy specimen of the laryngeal wall was taken blindly and was reported to show, "chronic inflammation and glandular epidermization."

Aspiration of the cyst was done next and revealed it to be a gas-filled sac. A diagnosis of external laryngocele was made. The next day the sac had filled again, and the roentgenograms in Figure 2*A* and *B* were made.

The patient underwent operation on Feb. 26, 1958. Preliminary to anesthetic intubation, it was again noted that the vocal cords were not visible because of local edema; there was no evidence of an internal component of the laryngocele; intubation was accomplished more or less blindly. An oblique incision was made parallel to the skin creases of the neck, across the prominence of the mass; the skin and platysma muscle were mobilized superiorly and inferiorly. The sternocleidomastoid muscle was retracted posteriorly, and the strap-muscles of the neck were retracted anteriorly, after which the entire mass was circumferentially dissected away from the adjacent structures. The superior pole of the thyroid gland was visualized inferiorly, the structures of the carotid sheath

Fig. 3.—Laryngocele exposed during surgery. The patient's head is at the left upper corner of the picture; the sternocleidomastoid muscle and carotid artery are retracted below the cyst, and the stylohyoid muscle and posterior belly of the digastric muscle are seen above, to the left.

posteriorly, and the stylohyoid and posterior belly of the digastric muscle superiorly (Fig. 3). The neck of the sac was found to lie between the superior cornu of the hyoid bone, above, and the ala of the thyroid cartilage, below, with the superior laryngeal nerve acutely bowstringed across its upper surface. This finding, and/or the laryngeal edema, might well explain the patient's hoarseness. The neck of the sac was seen clearly to traverse the lateral part of the thyrohyoid membrane, through a slit-like aperture. The neck was clamped and divided. The stump remaining was closed with a transfixing suture of 000 chromic surgical gut, much in the manner of handling a hernial sac. The resulting stump was then buried and the thyrohyoid membrane and adjacent tissues closed over the stump in two rows with interrupted 000 chromic surgical gut. A drain was placed down in the depths of the incision and brought out through the lower end of the wound, which was closed in layers. Because of the marked edema of the larynx and glottis, it was felt advisable to perform a tracheostomy to help tide the patient over the immediate postoperative period.

Following surgery, the patient made an uneventful recovery; the tracheostomy tube was removed on the fifth postoperative day, and the wound rapidly closed itself. The patient was discharged on the 12th postoperative day. He has done well since then.

The pathologist's report follows. "The specimen consists of a saccular gray-white structure, measuring 5 cm. in its longest diameter, covered on its outer surface by a shaggy, coarse, red-tan tissue and lined on its inner surface by a smooth, glistening, white membranous structure. Histologically, the specimen consists of a cystic space lined by a single layer of columnar ciliated epithelium of respiratory type. Diagnosis: laryngocele."

Summary

The anatomy, etiology, diagnosis, symptomatology, complications, and treatment of laryngocele are briefly reviewed.

The external variety of laryngocele is an extremely rare entity.

A case of external laryngocele is reported in which the diagnosis was made preoperatively by aspiration of the cyst and by roentgenograms.

55 E. Washington St.

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Reconstruction with Loss of the Hyomandibular Complex in Excision of Large Cancers

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Surgeons treating large cancers of the head and neck find that tumors in two locations present particularly formidable problems. One of these areas is the base of the tongue, where large neoplasms are difficult to remove without sacrifice of the essential blood supply to both sides of the tongue. This results usually in total glossectomy and must often be followed by removal of the larynx, even though this important structure be entirely free of tumor. If laryngectomy is not performed, the patient may succumb to aspiration pneumonia, due to inability to keep food and saliva out of the trachea in the absence of a tongue.

A second particularly troublesome tumor is one that involves the symphysis of the mandible and related muscles supporting the hyoid bone, larynx, and tongue. Removal of this important functional unit may leave the patient unable to breathe by way of the larynx and unable to swallow by mouth without aspiration. Again, laryngectomy of an essentially normal larynx may be resorted to in order at least to permit the patient to take food by mouth and handle his normal salivary secretions.

The surgeon must remain constantly critical of any operation whereby he finds himself removing nondiseased anatomy simply because he cannot reconstruct that region adequately to permit structure to function with usable efficiency and safety. As long as excision offers our first line of attack against head and neck cancer, surgeons will be challenged to find ways of limiting the deformity to that necessary in the actual removal of the tumor. It may be a long time before surgeons learn to reconstruct living functioning vocal cords—but it may be a much simpler matter to find ways of saving a larynx that would be removed by present-day methods.

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Anatomy

An understanding of the anatomy is essential to explain the functional losses one sees with modern cancer surgery. In the human, the base of the tongue, the hyoid bone, and the larynx are suspended directly above one another in a vertical column (Fig. 1). This column is spaced about equidistant from the symphysis of the mandible, the

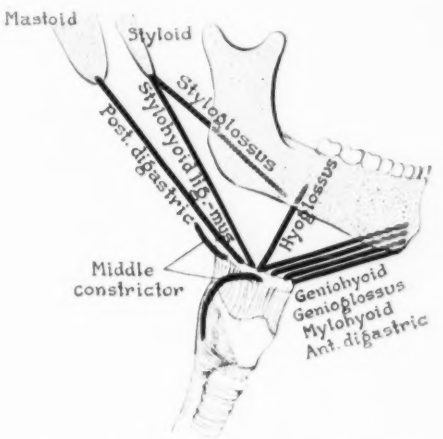


Fig. 1.—Lateral diagram to illustrate support and lifting mechanisms acting on the normal hyolaryngeal unit. Each dark line represents the direction of lift of a given pair of muscles. Note the effect of "balanced suspension." In addition, the thyrcohyoid muscles (not shown) tend to assist the anterior muscle group in drawing the larynx forward, away from the posterior wall of the cervical portion of the esophagus to allow the food to pass.

angles of the mandible, and the anterior bodies of the cervical vertebrae. In the act of swallowing, the hyoid bone and larynx rise about 2 cm., and the epiglottis turns downward and backward as the vocal cords close. In breathing, on inspiration, the infrahyoid muscles return the larynx and hyoid bone to their more caudad position, and the cords open. These complex and beautifully synchronized reflexes require accurate sensation over the base of the tongue and entrance to the larynx, as well as an orderly sequence of muscular contraction to position tongue, epiglottis, and vocal cords.

Swallowing of liquids in the human and the dog is normally brought about, first, by a strong contraction of the mylohyoid muscles. This causes a squirting action and forces the fluids downward into the lower esophagus *without* the aid of any peristalsis. If the mylohyoid muscle has its nerve supply divided, the patient must then raise the head to a vertical position in order to swallow liquids. Raising the head to swallow is also necessary in normal fowl or geese, where there is no "mylohyoid squirt" mechanism.

With solid food, the bolus is first poised on the tongue base; the mylohyoid muscle contracts, presses the tongue base against the palate and lifts the hyoid bone and larynx (Fig. 1). In this action the mylohyoid is assisted by the digastric, geniohyoid, and genioglossus muscles. The food is then propelled into the pharynx by a drawing backward of the tongue by the hyoglossi, glossopalatini, and styloglossi, and one understands why surgical removal of these muscles may particularly affect the swallowing of *solid* food. Normally a pressure of 20 cm. of water is developed in the posterior oral cavity. If the levator veli palatini and tensor veli palatini muscles have not been removed, they then raise the central portion of the soft palate to prevent regurgitation of the food into the nasopharynx.

The thyreohyoid muscles then raise the larynx and thus protect the entrance of the cords from descending food. The epiglottis is not a critical safeguard, as its removal is usually not accompanied by aspiration into the trachea. At the exact time of larynx elevation there is a reflex closing of the vocal cords. "The arytenoid cartilages are drawn forward from their usual positions against the posterior pharyngeal wall and rotated medially. This maneuver has the two-fold effect of closing the glottis *and causing the upper opening of the esophagus to gape.*" [5] Unless the larynx can be drawn forward and upward by the action of the geniohyoid, genioglossus, thyreohyoid, and anterior digastric muscles, it is difficult, if not impossible, to force food down the esophagus without its overflowing into the trachea.

The afferent nerve fibers of the swallowing reflex in man are the glossopharyngeal nerves and the pharyngeal and internal laryngeal branches of the vagus. If the mucosa, innervated by the internal laryngeal nerve, is stimulated by light touch with a cotton applicator, the stimulus will immediately initiate the complete swallowing reflex. The glossopharyngeal nerve contains those fibers through which the inhibition of respiration is brought about immediately during the descent of food through the upper esophagus. This respiratory inhibition will occur during either inspiration or expiration. Cocainization of the mucosa of the larynx and tongue base makes deglutition almost impossible. Markwald has found that the afferent impulses for swallowing reach a center near the vagus nuclei in the brain, just above the respiratory center, and are here relayed to the motor nuclei.

Surgical Implications

In the absence of actual involvement by tumor, functional disabilities in breathing and/or deglutition may follow operations

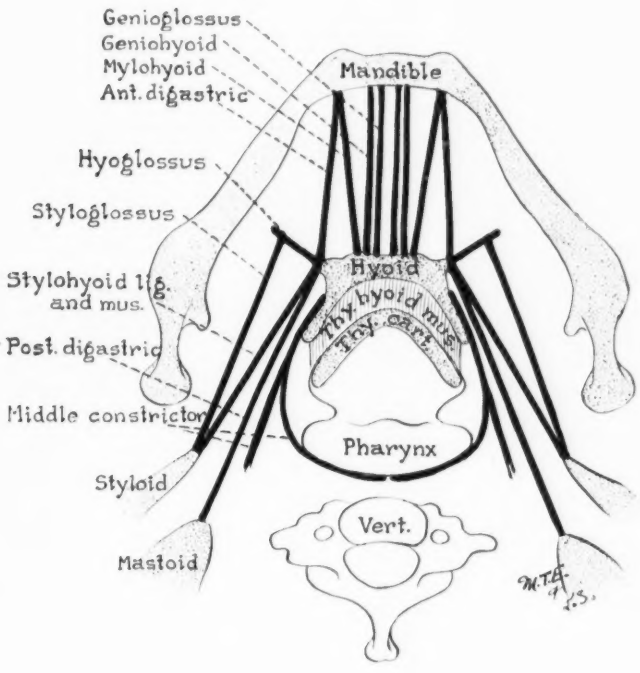


Fig. 2.—Diagram showing the major elements in the suspension of the normal larynx. It represents a cross section through the neck at about the level of the hyoid bone. Muscular or ligamentous vectors are shown by single dark lines. Note the grouping of anterior supports in the region of the mandibular symphysis. If these are removed, the larynx tends to lie back against the posterior wall of the esophagus and is not elevated in swallowing. Support in a neutral position gives any remaining musculature a chance to be more effective. After a cancer operation, the closure of skin flaps running from the mandible down to the laryngeal region may provide considerable substitute support, if the muscle removal has not been excessive.

for cancer on or about the "hyomandibular complex,"* for one of the following reasons.

1. The sensory nerves (internal laryngeal) may be injured by the surgeon in removing a cancer or carrying out pharyngotomy. This removes the "watchdog of the larynx," and aspiration with pneumonia may appear in the postoperative period. In the elderly patient even the loss of the internal laryngeal nerve on *one* side may make laryngectomy necessary. The surgeon is sometimes unaware of the proximity of these nerves to the hyoid bone; in removing that structure, the nerves will be found just under the mucosa and almost in contact with the inferior border of the hyoid.

2. The sensory nerves may not actually be cut by the surgeon; but if enough of the muscular and ligamentous supports to the larynx are cut, this structure may sag in the postoperative period and produce a bilateral or unilateral traction palsy of the internal laryngeal nerve that may be quite permanent.

3. Motor nerves to the vocal cords may be injured. The recurrent nerves are rarely injured in the resection of oral-cavity cancers in the larynx and trachea are saved. It is necessary on rare occasions, however, to sacrifice a single vagus nerve in the neck because of metastases, and this may cause an important cord palsy. Hemilaryngectomy is often performed for early carcinoma of the larynx and, of course, is usually well tolerated by the patient, even if one arytenoid cartilage has been removed. However, if the patient has had a total or subtotal glossectomy, or if he has postsurgical glottic ptosis, the vocal cords must close almost perfectly to prevent aspiration.

4. After removal of some of the upper supports of the hyomandibular complex, the larynx may have an intact nerve supply and

* We have chosen the term "hyomandibular complex" to refer to the closely connected unit of larynx and hyoid bone and its supporting muscles leading to the mandibular, mastoid, and styloid processes.

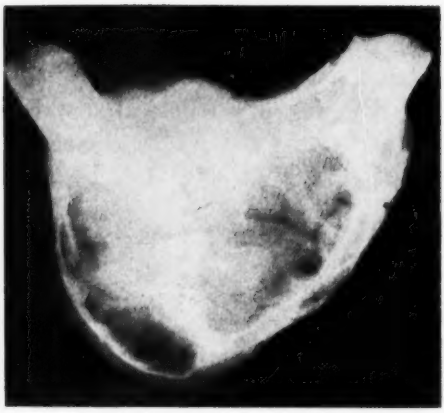


Fig. 3A.—X-ray of removed mandibular symphysis in an elderly woman to show need for resecting full thickness of the mandible and all muscles of the medial hyomandibular complex.

Fig. 3B.—Above, the removed (adamantinoma) and mandible may be seen, with involved skin and mucosa attached. Below, the immediate reconstruction has been carried out with a three-layered autogenous iliac-bone graft, and a transosseous steel bar for early fixation in this edentulous patient. A small wire strand runs from the mandible, on one side, down around the hyoid bone and back up to the mandible on the opposite side. This returns some of the support for the larynx and helps to ensure that no tracheostomy will be needed in the postoperative period.

may possess moderate support in a neutral position, but the muscular elevators may be missing or too weak for normal deglutition (Fig. 2). These patients can usually breathe adequately and manage to swallow their saliva. Ordinarily, they can take solid food, but tend to aspirate liquids into the trachea on occasion. Such patients tend to be apprehensive about eating and complain

Fig. 3C.—Postoperative views of the patient four years later. No late reconstruction was required. The steel bar is still in place, and the graft shows good bony union. There was no difficulty with swallowing or breathing, even immediately after operation.

of a good deal of coughing. Some will even resort to passing a tube into the esophagus for each meal. They usually "get along"—but not very satisfactorily (Figs. 3A-3C).

5. The tumor resection may have left the patient with almost no superior attachments for the larynx, so that it is allowed to settle backward and downward below the neutral position, or, in the case of some unilateral lesions, it may be drawn severely to one side by contracting scar (Figs. 4A and 4B).

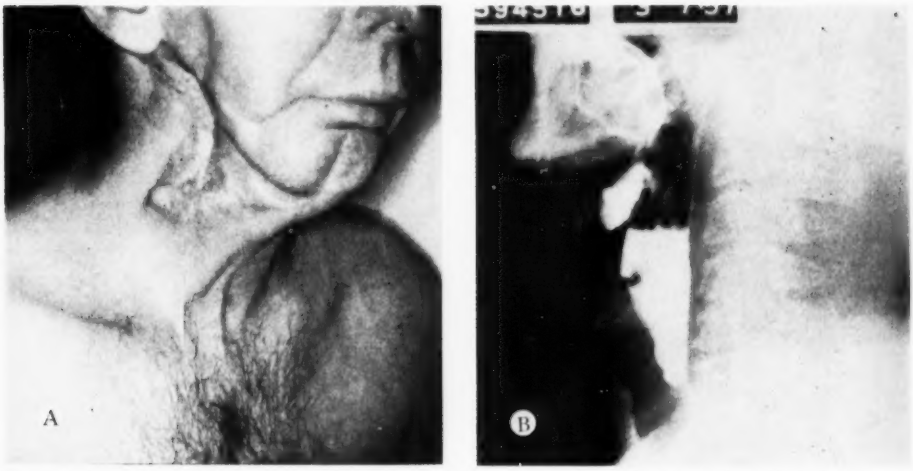


Fig. 4A and 4B.—View of neck in patient who had had a combined resection of carcinoma of the right floor of the mouth and the nodes of the neck six years previously. The prominence in the midportion of the right side of the neck is the right superior horn of the thyroid cartilage, giving some idea of the rotation and ptosis of the larynx. This produced angulation of the cervical portion of the esophagus and almost complete obstruction (Fig. 4B). It resulted from wide removal of the medial and right lateral laryngeal supports (including the right stylohyoid ligament and muscle) and cervical fibrosis adding to the drawing down of the larynx after operation. Figure 4B is an x-ray with iodized oil U. S. P. (Lipiodol) swallow to show esophageal obstruction at the level of the seventh cervical vertebra.

Fig. 5A.—The patient had a large carcinoma of the floor of the mouth, involving the mandibular symphysis, with bilateral cervical metastases. Here an apron flap of non-hair-bearing skin is turned under the skin of the upper neck 10 days prior to removal of the tumor.

Fig. 5B.—The specimen had been removed, including the anterior half of the tongue and the lymphatics of the left side of the neck (1949). A radical neck dissection was performed on the right side of the neck six weeks later.

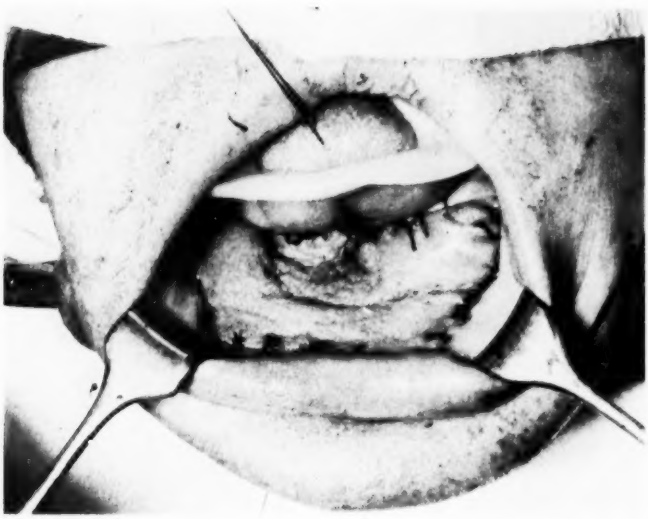
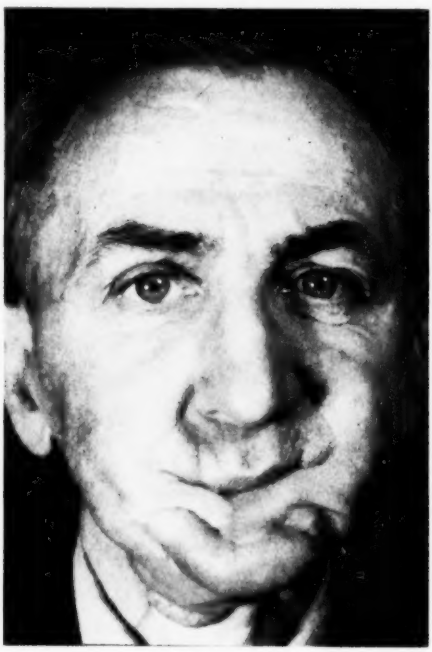


Fig. 5C. — The lining neck flap has been swung into the mouth *at the time* of tumor resection in order to close the fistula and prevent binding of the tongue base to the lower lip.

Fig. 5D.—The immediate flap permitted use of a steel bar to maintain normal separation of posterior-jaw fragments, and a single steel wire can be seen in the x-ray, where it runs from the steel bar down around the hyoid bone to support the larynx. The patient's tracheostomy stoma was corked off 24 hours after operation.

Fig. 5E.—The same patient as that shown in Figures 5A-5D. He has been well nine years since resection. He is still eating by mouth, without aspiration, and has satisfactory breathing and speech.



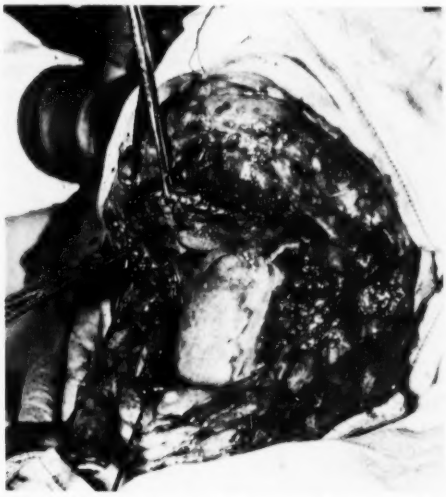
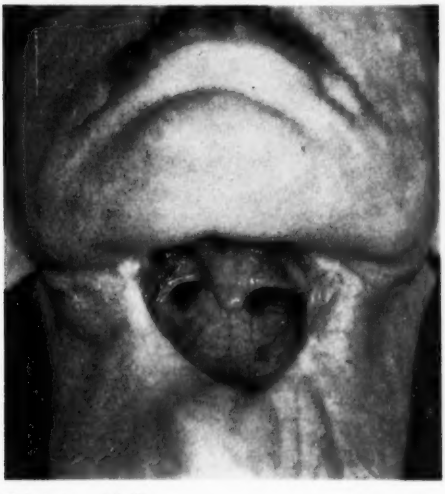


Fig. 6A.—Patient with huge carcinoma of the base of the tongue, requiring total glossectomy, in 1950. The posterior pharyngeal wall may be seen. The larynx was left in, but all superior supports were resected.

In both instances the patient is unable to swallow by mouth, but the mechanisms are different. If the glottis is drawn to one side, it may carry the esophagus with it and cause angulation with obstruction. The patient may then give a history of aspiration

Fig. 6B.—On healing, a large cervical fistula is seen with uvula and soft palate visible. Today we would run a suspension wire from one angle of the mandible to the larynx and back up to the opposite mandibular angle to prevent fixation of larynx in ptosed position.



if swallowing of liquids is undertaken without first extending the head on the neck.

If the glottic ptosis is bilateral, the patient is unable to "open" his upper esophagus to receive food; and if a total glossectomy has been performed, the patient lacks the ability to force food or fluid down the esophagus, the food enters the larynx, and severe coughing follows, even though the vocal cords may close properly. The picture is one of complete obstruction of the esophagus at the level of the cricoid, but an esophagoscope may readily be passed into the stomach without encountering any sig-

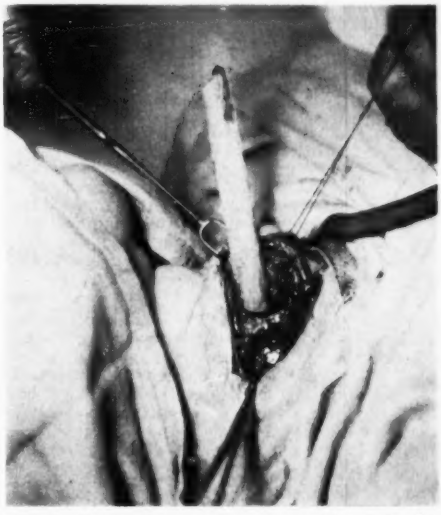


Fig. 6C.—Late correction was achieved by inserting two rib grafts in the neck. These were wired behind to the transverse processes of the cervical vertebrae, and the anterior ends were lashed together over the larynx, with the latter pulled forward so as to open the cervical esophagus (diagram, Fig. 6D). In this view the rib has been wired posteriorly but has not yet been cut off at the proper length anteriorly.

nificant resistance (Figs. 5A-5E and Fig. 6A-6D.) If the scar is not too fixed, the larynx may be drawn forward, and if swallowing is then successful, bone grafts may be used between the larynx and the cervical vertebrae to maintain a fixed lumen in the cervical esophagus (Fig. 6D).

6. Partial ankylosis of the arytenocricoid joint may occur as a result of previous irradiation therapy, or perhaps as a result

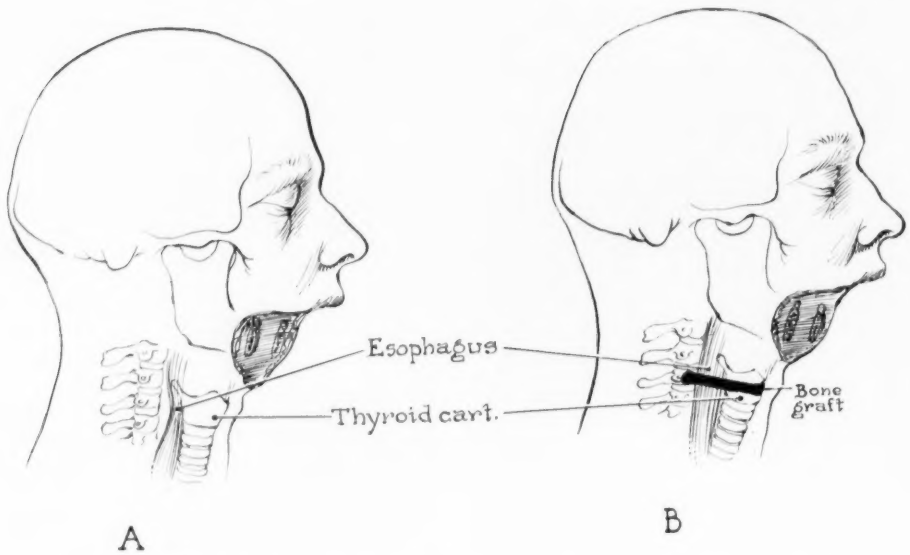


Fig. 6D.—Method of *late* correction of laryngeal ptosis due to surgical damage to the hyomandibular complex. (*A*). It is impossible for such a patient to elevate the larynx away from the vertebral column in swallowing, and aspiration is common. Once the bone graft is in place (*B*), the esophagus remains open, and the patient may again swallow by mouth, even in the presence of total glossectomy (Figs. 6A-6C).

Fig. 7.—This patient had arytenoid ankylosis following a combination of irradiation therapy and total glossectomy for carcinoma of the tongue. To prevent continuing aspiration, the vocal cords have been exteriorized by dropping a skin flap behind the posterior commissure. The mucous membranes remained pink and the cords moved well on phonation, but the ankylosis did not improve and the patient ultimately resorted to esophageal speech.

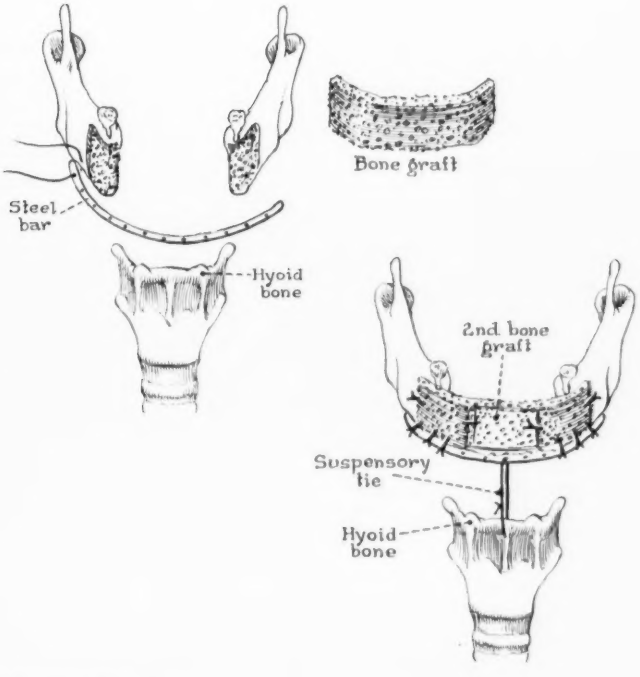
Fig. 8A.—This patient had carcinoma of the lip, chin, and mandible, with metastasis to the right side of the neck. Removal of the hyomandibular complex included the hyoid bone and symphysis but left the stylohyoid ligaments (for partial support of the larynx) and most of the tongue (to initiate swallowing in absence of the mylohyoid muscles).

Fig. 8B.—Immediate repair of the patient in Figure 8A was carried out with a nondelayed bitemporal flap. No wire or bone graft was needed. The tracheostomy and esophagostomy shown were not needed after three days, and the "skin sling" alone prevented dropping of the larynx.

of endotracheal anesthesia. If this complication occurs in conjunction with surgical removal of most of the tongue or with inability of the patient to elevate his larynx in swallowing, it is quite likely that continued aspiration of food into the trachea will result. Prevention is better than treatment for this condition. Avoidance of heavy irradiation to the arytenoid region and the practice of performing a tracheostomy under local anesthesia *without* initial laryngeal intubation for induction of anesthesia will greatly reduce the trauma to the larynx.

Exteriorization of the larynx may prove to be of some benefit for established cases of arytenoid ankylosis, and we were pleased to note in one such case that the vocal-cord mucosa tolerated the low humidity of room air very nicely (Fig. 7).

7. Rarely, a patient may be unable to swallow for a psychogenic reason. This



. Fig. 8C.—Diagram to show one satisfactory method of regaining support and jaw contour after surgical removal of the hyomandibular complex. This "bar and bone" technique (Figs. 3A-3C) is most helpful in the elderly patient, even if one has been able to preserve the lateral stylohyoid muscles and ligaments.

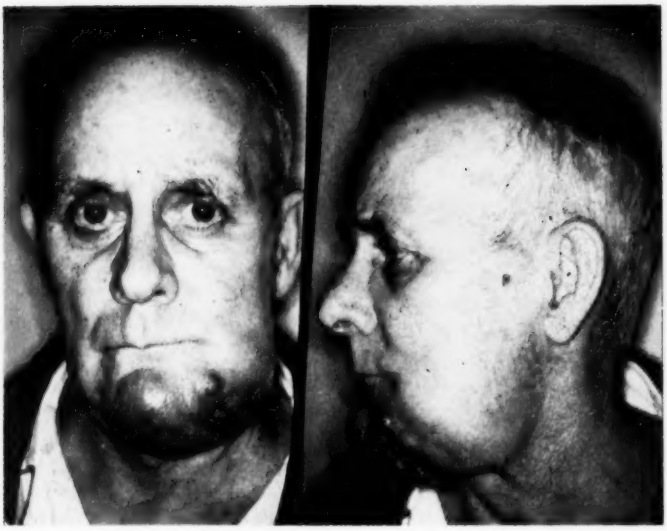


Fig. 9A.—Squamous-cell carcinoma of gingiva, with destruction of the mandibular symphysis, the anterior half of the tongue, and the skin of the chin and upper neck. Cervical metastasis is present.

may be a globus hystericus, an obsession that he still harbors an obstructing cancer in his throat, or a more complex psychosis. This condition will usually respond to reassurance and demonstration of patency of the esophagus.

Fig. 9B.—Tumor was removed in continuity with a bilateral neck dissection. Total mandibulectomy has been performed. The dorsal layer of tongue mucosa has been saved at this point, but need to resect both lingual arteries resulted in slough of this bit of remaining tongue.

8. Finally, it should be emphasized that a combination of the above factors may be working to produce problems in any given patient. Mucous-membrane closure after operation for cancer plays a role of little importance in support of the larynx, but skin closure may be much more critical than surgeons have realized. If large skin defects of the chin and lower lip are created in removing cancer of the hyomandibular region, it is possible to design an immediate reconstruction that not only will supply the needed skin but also will give a "skin sling" support and prevent the malpositioning of the larynx and its inherent functional difficulties. If the stylohyoid ligaments and muscles of the tongue base (styloglossus and glossopharyngeus muscles) can be preserved (Figs. 8A-8C), the skin sling alone will give the patient almost normal speech, breathing, and swallowing. But if the lateral and medial supporting elements of the hyomandibular complex are all sacrificed, the patient will require not only a skin sling but also some additional forward support, such as is provided by late bone-grafting of the chin, steel-wire suspension rigs, bone and bar units, or a similar arrengement to maintain the larynx in a semielevated position (Fig. 8C).

Fig. 9C.—Marked "Andy Gump" deformity on healing. Margins of specimen were reported "free of tumor" by pathologists. Outline of large temporal artery flap may be seen on the forehead. This was "delayed" at time of primary resection.

Fig. 9D.—Condition of patient only 12 days after primary resection. The bipedicled flap has been shifted down and folded on itself to furnish both skin and lining for the floor of the mouth. The forehead was given a split graft at this time.

The most complex problems arise when tumor removal requires wide removal of skin, as well as all lateral and medial supporting elements of the hyomandibular complex (Figs. 9A-9E). Here the use of immediate or early reconstruction with a scalp or forehead flap will control salivation, reduce the distortion of contracture, facilitate feeding, and give some return of voice; however, if the patient is to swallow without coughing and breathe easily when lying flat on his back, some plan must be devised for additional forward support of the tissues of the chin and upper neck. The patient shown in Figures 9E and 9F showed difficulty in breathing only when supine, and this was readily relieved by forward traction on the chin flap. He also tended to aspirate

Fig. 9E.—Strips of polyvinyl alcohol sponge may be seen placed beneath the chin flap to prevent early contracture in the chin region. The lower folded edge of the flap was next divided. The deep layer was sutured to the tongue and the external layer of the skin of the neck. Both pedicles were then divided and implanted. Patient is still free of disease 16 months later.

when swallowing, and this, too, was completely relieved by slight forward and upward support of the chin. Bone grafting to reconstruct the lower jaw was thus indicated in this instance.

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Congenital Absence of the Gallbladder

Diagnosis by Operative Cholangiography

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Congenital absence of the gallbladder is a very rare occurrence, most cases of which are found at autopsy. Dixon and Lichtman,[2] in 1945, were able to find 60 well-documented cases in the literature to that date, 24 of which were discovered at operation. In 1949 Hillemand, Rosenstiel, and Brule[6] found a total of 86 cases, 36 of which had been diagnosed at operation. Malmström,[11] in 1953, was able to find five more operative cases, including one of his own, and Polivy and Sachs,[12] in 1954, reported one more, bringing the total number to 42. The frequency of occurrence of this anomaly in autopsy series is variously reported to be from 0.03% to 0.09%, but is more likely closer to the lower figure.

Twenty-six animal species, including certain herbivores, marsupials, and rodents, normally have no gallbladder. Though it was formerly thought that fetal peritonitis, syphilis, and a few other obscure entities were the cause of congenital biliary-tract malformations in humans, the etiology is now generally conceded to be on the basis of a failure of development of the embryonal gallbladder bud. In most instances the agenesis is complete, including absence of the cystic duct, but a few cases have been reported in which a vestigial cystic-duct stump was present. Most authors have described the presence of minimal to extensive adhesions in the hepatoduodenal area, the significance of which is not clear. That agenesis of the gallbladder may be inherited must be borne in mind. Kobacker,[8] in 1950, reported the histories of two sisters who were operated upon for biliary symptoms, in each of whom no gallbladder was found. Three of five other siblings, and two descendants, of these two proved cases had nonvisualizing gallbladders on cholecystography, a finding which was thought to be presumptive evidence of agenesis of the gallbladder.

About one-half the patients found to have this condition complain of symptoms suggesting biliary disease, the remainder of cases being found incidentally at surgery. Interestingly enough, agenesis of the gallbladder is found clinically about twice as often in female as in male patients, paralleling somewhat the general incidence of biliary-tract disease. Most of the surgical reports concern patients operated upon for assumed cholecystitis or common-bile-duct obstruction. Review of the recorded cases reveals that about half have had jaundice at the time of surgery or a previous history of jaundice.

Diagnosis of this anomaly has never been —indeed, cannot be—made preoperatively. At the time of surgery very complete exploration of the biliary tree must be carried out, as a gallbladder almost or completely buried within the substance of the liver may otherwise be missed. For this reason the most reliable method of demonstrating true agenesis of the gallbladder is by operative cholangiography. Even open common-duct exploration does not provide as adequate a picture of the biliary radicles, especially within the liver, as does cholangiography. Survey of the literature reveals that the injection of a contrast medium through an indwelling T-tube has been performed only seven times previously, and cholangiography at the time of operation has been performed only once, in the investigation of agenesis.

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Malmström reported in 1953 the first case of complete absence of the gallbladder proved by operative cholangiography.

When this condition is found at surgery, Dixon and Lichtman,[2] and others, recommend prolonged T-tube drainage, for up to two years, especially with the finding of dilated extrahepatic ducts, jaundice, or pancreatitis. No conclusion can be drawn from the literature regarding the occurrence of compensatory dilatation of the biliary duct system of patients with congenital absence of the gallbladder. The frequency of dilatation of the extrahepatic biliary ducts is reported to vary from 15% to 50%, but in many cases a description is not given. The fact that stones have been found in one-half of all reported cases in this condition with dilated extrahepatic ducts is proof, as Polivy and Sachs point out, that the presence of the gallbladder is not necessary for the production of biliary-tract calculi.

The following case report is of a patient operated upon because of symptoms simulating gallbladder disease, in which the diagnosis of complete absence of the gallbladder was made and proved by cholangiography at the time of surgery. This is the second reported instance of such a procedure.

Report of a Case

A 36-year-old man, a bookkeeper, was admitted to Sequoia Hospital, Redwood City, Calif., on Feb. 15, 1955, because of upper abdominal discomfort.

The patient stated that he had noted indigestion due to fatty foods for a number of years, probably since young adulthood. Although this symptom had been noticeable and somewhat annoying, it had never previously been incapacitating. For the month prior to admission, however, there had been gradually increasing epigastric aching pain and some right-upper-quadrant pain. This was aggravated by fatty-food intake but did not respond to a bland ulcer diet. There was never any sudden severe pain, nausea or vomiting, or fever.

The past history and the family history revealed nothing contributory. There was no known family history of gallbladder disease, and no previous abdominal operation.

Physical examination at admission revealed a well-developed and well-nourished man, in no acute distress. The heart and lungs were clear. The positive physical findings were limited to the abdomen, where there was a mild uneasy feeling on pressure in the epigastrium and the right upper

Operative cholangiogram showing complete absence of the gallbladder or cystic-duct remanant.

quadrant. There were no palpable organs or masses.

Oral cholecystography, performed on Feb. 16, and repeated on Feb. 17, failed to visualize the gallbladder. Gastrointestinal series and barium enema x-ray studies were normal. Because of the long history of fatty-food intolerance, the more recent exacerbation of epigastric and right-upper-quadrant pain, and the persistently nonfunctioning gallbladder on attempted cholecystography, a diagnosis of chronic or subacute cholecystitis was made and cholecystectomy was planned.

The patient was taken to surgery on Feb. 21, and the abdomen was opened through a right subcostal incision. Complete abdominal exploration failed to reveal any abnormality other than that the gallbladder could not be found. There were a very few fine, filmy adhesions in the hepatoduodenal area, but no cord of tissue or stump was present to reveal the site of a vestigial gallbladder. The common bile duct and right and left hepatic ducts were exposed from the pancreas to the liver, and no gallbladder was found. The extrahepatic biliary ducts did not appear grossly dilated. The common duct was opened and extensive tactile exploration carried out, no abnormality being found. A #10F T-tube was inserted and cholangiography immediately carried out, using 35% iodopyracet (Diodrast). Excellent visualization of the biliary tree from the small hepatic radicles to the duodenum was obtained, and no evidence of gallbladder or cystic duct stump was found (Figure). The radiologist reported that the common duct was slightly larger than usual. After appendectomy, the wound was closed in layers.

The patient made an uneventful recovery. The T-tube was clamped on the sixth postoperative day, and the patient was discharged from the hospital on the eighth postoperative day. The T-tube was removed on the 14th postoperative day, and the patient has been asymptomatic since that time. Follow-up reports indicate that the patient continues essentially asymptomatic, though he remains on a low-fat diet.

Summary

Congenital absence of the gallbladder is a rare anomaly. Though 43 cases have been reported to have been found at operation, none has ever been diagnosed preoperatively, and this article reports the second case to have been proved at the time of surgery by operative cholangiography. Cholangiographic investigation is probably the only possible means by which a definite diagnosis of agenesis can be made. In the presence of dilated extrahepatic biliary ducts, jaundice, or pancreatitis, prolonged T-tube drainage of the biliary duct system is suggested until the duct system reverts to normal size.

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Congenital Absence of the Gallbladder

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Variations and anomalies of the biliary system and related blood vessels are relatively common, occurring in 10% of necropsy specimens.[1] However, absence of the gallbladder without associated defects of the biliary tract is an exceedingly rare finding, the incidence being reported as 0.065% by Tallmadge,[2] who found 12 cases in a collected series of 18,350 necropsies, and as 0.04% by Mouzas and Wilson,[3] who reported 9 cases in 21,631 necropsies. We wish to report a case, confirmed by operative cholangiographic examination, and to review briefly the pertinent literature and practical aspects of this condition.

In 1928, Bower[4] reviewed 31 cases of congenital absence of the gallbladder and cystic duct. In 1936, Gross[5] reported 38 cases, and Finney and Owen[6] added 10 cases in 1942. A review of this subject by Dixon and Lichtman[7] in 1945 included 50 cases reported since 1900 and 10 cases from the records of the Mayo Clinic. In 1947, Latimer, Mendez, and Hage[8] found reports of 71 cases in the literature and added 3 cases of their own. Iovetz-Tereshchenko[9] reported a case in 1955 and, after a "short but reasonably thorough search," found reports of 29 cases for the period of 1947 to 1955. Also in 1956, Jutras and Rice[10] reviewed the literature and found reports of 115 cases, including their case report. A search of the available recent English-language literature revealed an additional six cases.[11-16] So, to the present time, the total number of reported cases is approximately 122.

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An abnormality in embryonic development of the biliary tract is now generally accepted as the cause of this anomaly. Gross[5] stated that absence of the gallbladder may be explained in two ways: 1. The hepatic diverticulum, a sacculation formed from the foregut, consists of a cranial portion, which will differentiate into the glandular tissue of the liver and its bile ducts, and a caudal portion, which becomes the gallbladder and cystic duct. Failure of this caudal outpocketing of the hepatic diverticulum to develop would result in complete absence of the gallbladder and cystic duct. 2. In the development of the gallbladder and extrahepatic biliary ducts, these structures are hollow initially, but later their lumina become obliterated temporarily as they pass through the so-called solid phase. Failure of reestablishment of the lumina of the gallbladder and cystic-duct portions would result in their absence, or they would be represented by a solid cord rather than a hollow organ.

Report of a Case

A 29-year-old white man was first seen in the military dispensary at Goodfellow Air Force Base, Texas, in January, 1957, because of upper abdominal discomfort. He complained of epigastric fullness and bloating with the desire, but the inability, to belch. The symptoms occurred shortly after the evening meal, which had been highly seasoned. There was no nausea or vomiting. The results of examination were not remarkable except for vague discomfort on palpation of the upper part of the abdomen, especially on the right side. Further questioning revealed that for approximately one year he had been experiencing intermittent bouts of postprandial bloating and fullness, which were becoming increasingly frequent and severe, and that there was a definite history of intolerance of fatty food. On cholecystographic examination with the dye given by mouth, the gallbladder was not visualized. This procedure was repeated with a

double dose of the dye (12 tablets [6 gm.] of iopanoic acid U. S. P. [Telepaque]), and again the gallbladder was not visualized. It was decided to try medical management of the patient, and he was started on therapy with a low-fat diet and antispasmodics.

He was seen again in March, 1957. Because his dyspepsia was becoming increasingly severe in spite of dietary measures, he was admitted to the hospital for cholecystectomy. He denied back pain or true colic and gave no history of fever, chills, jaundice, dark urine, or acholic stools. A severe attack was occasionally followed the next day by soreness in the right upper quadrant of the abdomen.

The family history revealed almost identical gastrointestinal symptoms in his father and older brother. The patient had had an induction and several reenlistment physical examinations, and the results of all of these had been negative. At the time of hospitalization the physical findings were again within normal limits. There were no abdominal scars, and there was no previous history of an abdominal operation.

The results of laboratory studies, including a complete blood count, urinalysis, serologic test for syphilis, determination of serum bilirubin by the direct and indirect reactions, and cephalin-flocculation test, were within normal limits. Roentgenographic examination of the thorax gave negative results. A third cholecystographic examination, again with a double dose (6 gm.) of dye given by mouth, failed to demonstrate any shadow that could be identified as that of the gallbladder. A plain roentgenogram of the abdomen revealed no calculi.

On April 4, 1957, the abdomen was explored on the basis of a preoperative diagnosis of chronic cholecystitis. Examination of the peritoneal cavity gave negative results except with respect to the biliary tract. No abnormalities of the pancreas were noted. The liver appeared grossly normal and presented no anatomic variations, except that no gallbladder was seen in the usual site. There were no adhesions or inflammatory changes in this region. The infrahepatic region was very carefully inspected, and, although there was a slight depression at the usual site for the fossa of the

Cholecystogram showing no trace of the gallbladder or cystic duct.

gallbladder, no structure was found which could be identified as a gallbladder. The common bile duct was then carefully dissected, beginning at the retroduodenal portion and continuing up into the hilus of the liver. The duct was normal in size, regular, and thin-walled. No stones could be palpated. The right and left hepatic ducts also were exposed and presented a normal anatomic arrangement. The hepatic artery was several times larger than normal and ran a very tortuous course to the liver. In order to verify the apparent absence of the gallbladder, a cholangiogram was then made by injecting 15 cc. of 35% iodopyracet (Diodrast) directly into the common bile duct through a small-bore needle. The biliary tree was satisfactorily visualized; it was interpreted as being normal except that there was no trace of either a cystic duct or a gallbladder (Figure). The dye passed freely into the duodenum, and there was no suggestion of biliary calculi. It was therefore concluded that we were dealing with a congenital absence of the gallbladder, and, after incidental appendectomy, the abdomen was closed.

The postoperative course was uneventful. The patient was started on treatment with a low-fat diet and a commercial preparation containing bile salts, pepsin, and pancreatin, to be taken with meals. One year after operation he wrote that he has noticed significant improvement. Only occasionally has he been disturbed by "indigestion," and only on one occasion has he suffered from a recurrence of his former symptoms, and even then the symptoms were mild. Unless we attribute his improvement to the postoperative use of the indicated medication, it is difficult to understand why medical management has been more successful since the exploration than it was before.

Comment

The average age of patients found to have this anomaly is 46 years.[7] In necropsy cases the incidence in males is the same as that in females. However, clinically it is twice as common in females, consistent with the usual sex ratio in surgical biliary disease as a whole.[8]

The symptoms and clinical findings in patients with congenital absence of the gallbladder are similar to those of patients with gallbladders that are nonfunctioning or poorly functioning because of disease. Of 34 surgical cases described by Latimer and associates,[8] the preoperative diagnosis was cholecystitis in 13 and obstruction of the common duct in 8. In the series by Dixon and Lichtman,[7] symptoms suggestive of cholecystic disease were present in 35 of the 60 cases (58%); the anomaly was symptomatic in 73% of the patients more than 45 years of age. Jaundice was present in 48% of the cases and choledocholithiasis in 27%. Abnormalities of the liver and pancreas are not infrequently associated with this anomaly; congenital variations, cirrhosis, hepatitis, and pancreatitis have been reported by several authors.[7,8,17] Dixon and Lichtman[7] found the common duct dilated in approximately half the cases in which it was mentioned, and the cystic duct was absent in 42 of the 46 cases in which this structure was discussed. The fossa for the gallbladder is usually absent.

Kobacker[18] has expressed the view that possibly heredity plays a role in the occurrence of this anomaly and cites the cases of two sisters who were found at operation to have congenital absence of the gallbladder. A study of five sisters of these two patients and the daughters of two of these siblings revealed that three of the five sisters and the two next-generation members had nonvisualization of the gallbladder on roentgenographic examination, and therefore presumptive evidence of agenesis of this organ. It is interesting that in our case the patient had said that his older brother and his father had symptoms very similar to his. However, cholecystographic examination of these relatives, with the dye given by mouth, revealed a normally functioning gallbladder without evidence of stones.

Congenital absence of the gallbladder is frequently associated with signs and symptoms of disease of the biliary tract, and a majority of the cases have been discovered at operation performed because of these symptoms. With this high incidence of symptomatic patients, it seems reasonable to assume, as has been suggested by various authors,[11,19] that congenital absence of the gallbladder may predispose to disorders of the otherwise intact biliary tree, particularly the common bile duct. In addition, the occurrence of symptoms typical of cholecystic disease in patients with congenital

absence of the gallbladder tends to substantiate the idea that these symptoms in patients with normal anatomic arrangements of the extrahepatic biliary tree are not necessarily dependent on the diseased state of the gallbladder alone, but may reflect the pathologic condition of the biliary duct system. Several observers [7,11,13,19] have stressed the rather frequent occurrence of disorders of the common duct in association with agenesis of the gallbladder. The exact disturbance in biliary dynamics and physiology, however, is unknown. Dixon and Lichtman [7] and Nelson and associates [13] discussed the similarity of symptoms in this anomaly to the clinical entities we refer to as the postcholecystectomy syndrome and biliary dyskinesia. In many respects, these disorders are similar, and the cause of symptoms in a great number of cases is obscure. Contrary to the belief that congenital absence of the gallbladder may affect the remaining part of the biliary tract adversely, Mouzas and Wilson [3] have expressed the view that its absence does not cause alteration in function of the biliary tract, and does not cause symptoms; that when symptoms do occur, they result from cholangitis or stone, and are similar to symptoms that occur in a patient with an intact biliary tree.

It is, of course, not surprising that the diagnosis of agenesis of the gallbladder has not been made preoperatively. Since the symptoms suggest disease of the biliary tract, and since a gallbladder is not visualized on cholecystographic examination, it is naturally assumed that the patient has chronic cholecystitis with a nonfunctioning gallbladder. Operative cholangiographic examination should always be made in such cases, not only to rule out intrahepatic or other abnormal positions of the gallbladder but also to visualize any calculi that may be present in the duct.

Because of the frequency of common-duct disorders and because of the occasional associated pancreatitis, the treatment advised by Dixon and Lichtman [7] is prolonged drainage of the common duct by means of a T-tube "even when the common bile duct is of normal size and stones are not found." Certainly, in those cases in which there is a history of jaundice or colic, dilatation of the common duct, or the presence of calculi, there is no question as to the need of choledochostomy with subsequent drainage. The problem for the surgeon arises, however, in those patients who are symptomatic and in whom the duct is found to be normal and without calculi. The reluctance on the part of the surgeon to carry out the above-mentioned procedures on these patients is understandable. For this reason, a review of the reported surgical cases was undertaken with the hope of arriving at some conclusion as to the operative procedure to be utilized in those patients in whom no clinical abnormalities of the common duct are found at the time of operation.

According to Latimer, Mendez, and Hage [8] (1947), 71 cases of congenital absence of the gallbladder had been reported, and of these, 34 cases were discovered at operation. In addition, 34 operative cases reported since then were available for review. Thirty-four (50%) of these surgical patients were found to have dilatation of the common duct or biliary calculi or both, and in almost every case in which follow-up data were included in the report these data indicated that the patients were free of symptoms after exploration and drainage of the common duct. In 17 of the reports (25%), information concerning the status of the extrahepatic biliary ducts or the postoperative course of the patient was lacking.

There were 17 symptomatic patients (25%) with this anomaly in whom the common duct was found to be normal and free of stones at the time of laparotomy. Because of associated diseases and complications, or because of the lack of sufficient information in the case reports, seven of these cases could not be properly evaluated. A study of the remaining 10 cases revealed the following information.

Three patients [7,18,20] were treated by exploration and drainage of the common duct and were subsequently asymptomatic. In

Dixon and Lichtman's Case 2, the T-tube was left in place for two years, despite the absence of stones or dilatation of the duct, and one year after its removal the patient continued to be free of symptoms. Two patients [9,21] underwent abdominal exploration because of their symptoms, but choledochostomy was not performed; they were asymptomatic when seen two and one-half and seven months, respectively, after laparotomy. The remaining five patients,[7,13,15,22] including our patient, also did not undergo exploration or drainage of the common duct at the time of operation, and in each case their symptoms continued postoperatively, although in four of the cases a variable degree of improvement was noted. As stated previously, it is difficult to understand why some improvement is observed following an abdominal exploration. Perhaps a stricter dietary and medical regimen is followed after the exact nature of the abnormality has been determined. In none of the cases studied did symptoms persist after drainage of the common duct.

With so few cases, it is obvious that no statistical significance could be attached to these findings. However, it appears that the suggested method of treatment—choledochostomy, with careful exploration for stones, and external drainage by means of a T-tube, even in the patient with an otherwise normal-appearing extrahepatic biliary tree—is sound and offers the best chance for the complete alleviation of symptoms.

Summary

In a case of congenital absence of the gallbladder the biliary tract was otherwise apparently normal. Operative cholangiographic examination is helpful in determining abnormal positions or absence of the gallbladder and the presence of calculi. Careful exploration of the common bile duct and T-tube drainage seem advisable even when the duct is not dilated and stones are not detected. Although statistical proof is lacking, such treatment appears to offer the greatest chance of alleviation of symptoms in congenital absence of the gallbladder.

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Addendum

Since this article was submitted, Pines and Grayzel (A. M. A. Arch. Surg. 77:171-180, August, 1958) have presented an excellent review of this subject in which one operative and four necropsy cases are described. They, too, agree that in the absence of any apparent pathologic change other than agenesis of the gallbladder, common-duct exploration and T-tube drainage are indicated. In a study of congenital anomalies of the gallbladder, Rabinovitch and associates (Ann. Surg. 148:161-168, August, 1958) found five cases of congenital absence of the gallbladder in their series as incidental findings at necropsy, four of which apparently were associated with an otherwise intact extrahepatic biliary-duct system.

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Pseudomembranous Enterocolitis

Are Antibiotics Wholly Responsible?

LIEUT. COL. ROBERT M. HARDAWAY III (MC), U. S. Army, and DONALD G. McKAY, M.D., Boston

It is widely accepted that the syndrome of pseudomembranous enterocolitis is due to a Staphylococcus enteritis secondary to administration of wide-spectrum antibiotics. However, in a previous paper [1] we showed that it is possible to reproduce consistently the pathology and many of the clinical manifestations of this syndrome in dogs (Figs. 1-8) in the absence of antibiotics or bacterial infection. This was done by means of an intra-aortic injection (through polyethylene catheters inserted in the femoral artery) of incompatible blood. There resulted an episode of intravascular clotting with the production of fibrin thrombi in the capillaries of the mucosa and submucosa of the bowel. This caused necrosis (due to ischemia) of the superficial mucosa and pseudomembrane formation. It has since been possible consistently to prevent the syndrome by preheparinizing the dogs. It was found that the lesions in the jejunum, ileum, and colon could be largely prevented by protecting the bowel from direct infusion of incompatible blood by occluding the superior mesenteric artery while the transfusion was entering the aorta [2,6] (Figs. 2 and 3). A bleeding tendency always accompanies the episode of intravascular clotting. This is due to (1) a drop in circulating fibrinogen and platelets and (2) the appearance of a circulating anticoagulant with some of the properties of heparin.[4-8] This work was done at the U. S. Army Hospital, Fort Belvoir, Va., and has been repeated during the course of other experiments at

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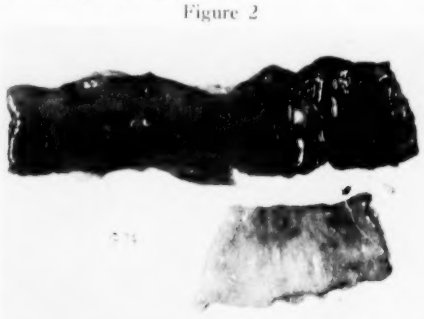
Fig. 1.—Kidneys (above), duodenum (second), ileum (third), and colon (below) of a dog which had been given an intra-aortic transfusion of incompatible (human) blood without occluding the superior mesenteric artery. Note the hemorrhagic necrosis throughout the bowel, but most prominent in the duodenum and ileum. There is a small amount of involvement of the large bowel.

Figure 1

Fig. 2 (Dog G74).—Hemorrhagic duodenum (above), compared with more normal ileum of dog dying in shock three hours after intra-aortic transfusion. Jejunum and ileum were protected by temporarily occluding the superior mesenteric artery during the transfusion.

Figure 2



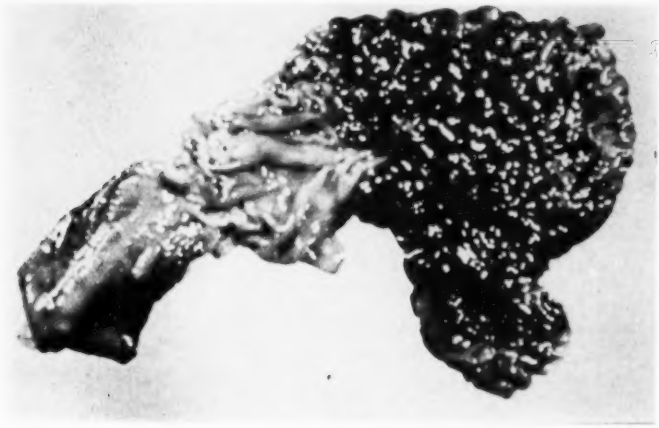


Fig. 3 (Dog G43).—Hemorrhagic mucosa of fundus of stomach of dog given intra-aortic incompatible transfusion. Antrum, pylorus, and first part of duodenum are normal. Dog died in shock after massive hematemesis. Superior mesenteric artery was occluded to protect intestine.

the U. S. Army Hospital, Frankfurt am Main, Germany.

It has also been shown [2] that it is possible to reproduce a similar clinical syndrome experimentally in animals by means of antibiotics and the production of a staphylococcic enteritis.

One would suppose that two such different etiologic agents would produce different clinical entities. Actually, this may be true. Most reported series of cases of pseudomembranous enterocolitis of any length are classified into severe and mild cases. Helmer,[3] in reporting 34 cases, separated them into 27 "mild" cases and 7 "severe" ones. The mild cases were characterized by a 24-hour period of *fever* and other signs of *infection*, with a moderate ileus. This was followed by a massive *diarrhea*, and in some cases not adequately treated, by signs of shock. Of the 27 cases, 25 recovered. The seven severe cases were all fatal, and the diagnosis was not made till after death. Those were characterized by the sudden onset of *circulatory collapse* and *death* within 24 hours in all but one case.

It is the purpose of this report to correlate experimental and clinical data and

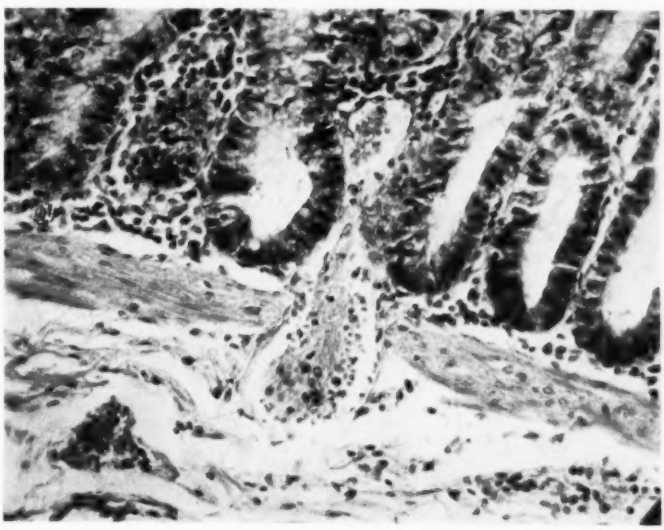


Fig. 4 (Dog 18).—Colon. Thrombus in capillary traversing muscularis mucosae. This is the earliest histologically detectable change in the experimental production of pseudomembranous enterocolitis. Hematoxylin and eosin; reduced from mag. × 240. Reproduced by permission of the Armed Forces Institute of Pathology, Walter Reed Army Hospital; AMH 15368, A.

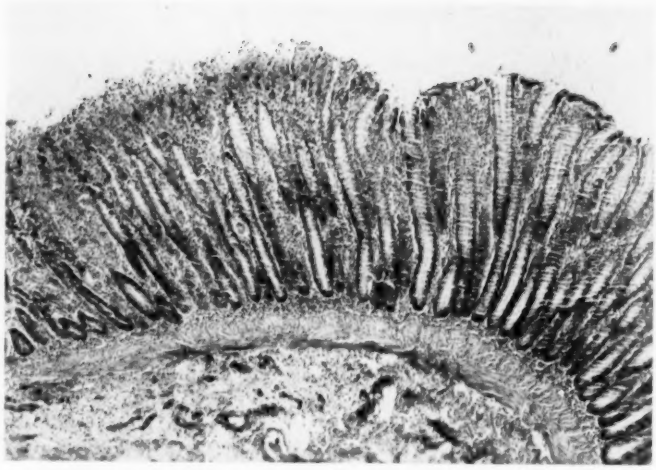


Fig. 5 (Dog 16).—Ileum. The mucosa on the right is intact. The superficial portion of the mucosa on the left is necrotic and hemorrhagic. One capillary thrombus is visible in the mucosa of the hemorrhagic area in this low-power photomicrograph. Hematoxylin and eosin; reduced from mag. × 50. Reproduced by permission of the Armed Forces Institute of Pathology, Walter Reed Army Hospital; AMH 15368, F.

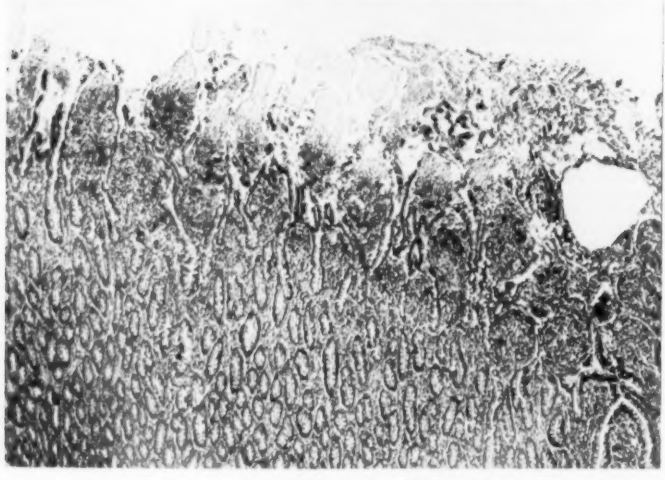


Fig. 6 (Dog 17).—Jejunum. The deeper portions of the mucosa are intact, but the tips of the intestinal villi are necrotic and the superficial epithelium has peeled off in chunks. Hematoxylin and eosin; reduced from mag. × 50. Reproduced by permission of the Armed Forces Institute of Pathology, Walter Reed Army Hospital; AMH 15368, G.

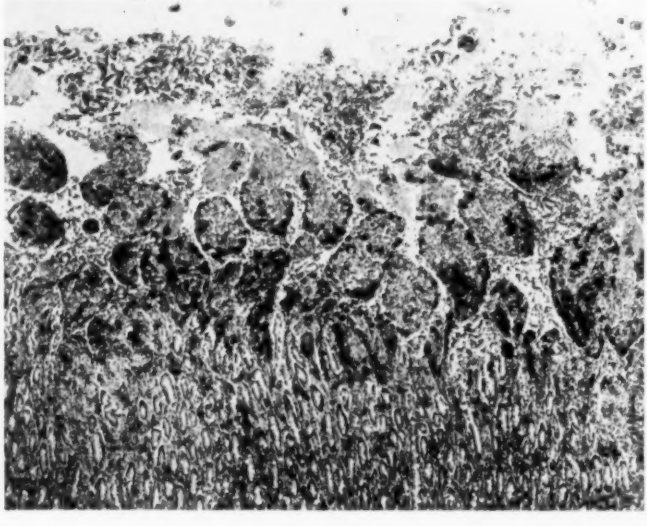


Fig. 7 (Dog 52).—Jejunum. The dark patches in this photomicrograph are masses of red blood cells. The tips of the villi are necrotic, and large masses of fibrin lie free in the lumen, surrounded by epithelial cells and leukocytes. This is the beginning of the formation of the pseudomembrane. Hematoxylin and eosin; reduced from mag. × 50. Reproduced by permission of the Armed Forces Institute of Pathology, Walter Reed Army Hospital; AMH 15368, J.

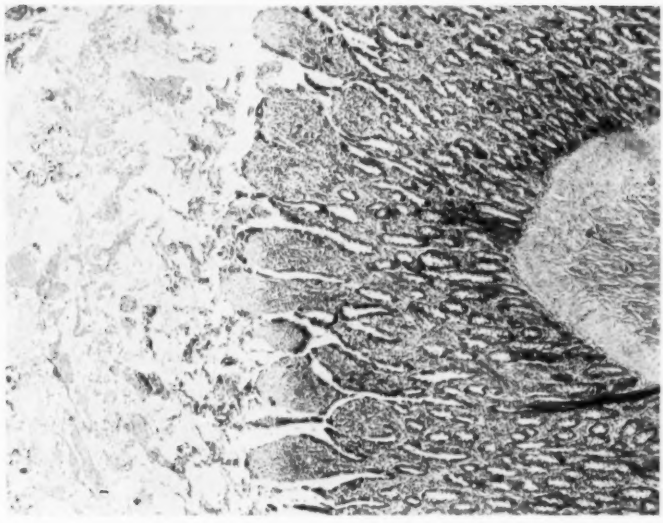


Fig. 8 (Dog 52).—Jejunum. The pseudomembrane is fully developed in this region and is composed of strands of fibrin, mucus, and desquamated epithelial cells. The tips of the villi are necrotic and hemorrhagic. Hematoxylin and eosin; reduced from mag. × 50. Reproduced by permission of the Armed Forces Institute of Pathology, Walter Reed Army Hospital; AMH 15368, H.

present evidence that the syndrome of pseudomembranous enterocolitis is not simply a Staphylococcus enteritis but a complicated syndrome due to at least two possible etiologic agents, and varying in its clinical manifestations.

Report of Cases

Cases Apparently Due to Intravascular Coagulation Alone

Case 1.—This 11½-year-old white girl was admitted to the U. S. Army Hospital, Fort Belvoir, Va., on July 6, 1955, with a complaint of vomiting and abdominal pain. The present illness started July 4, when the patient complained of a mild, but persistent stomach-ache. The next day vomiting started, and the pain became worse. The past history revealed an appendectomy in 1954.

On admission the patient was acutely ill. She was vomiting dark-brown material and showed signs of marked dehydration. The abdomen was distended, but no spasm could be elicited. It was moderately tender throughout to palpation. No peristalsis could be heard. Blood pressure was 80/60 and temperature 104 F.

An x-ray of the abdomen showed distended loops of small bowel. A diagnosis of intestinal obstruction was made.

Fig. 9 (Case 1).—The pseudomembrane lining the ileum is composed of fibrin, mucus, leukocytes, and epithelial cells. Hematoxylin-eosin stain; × 45.

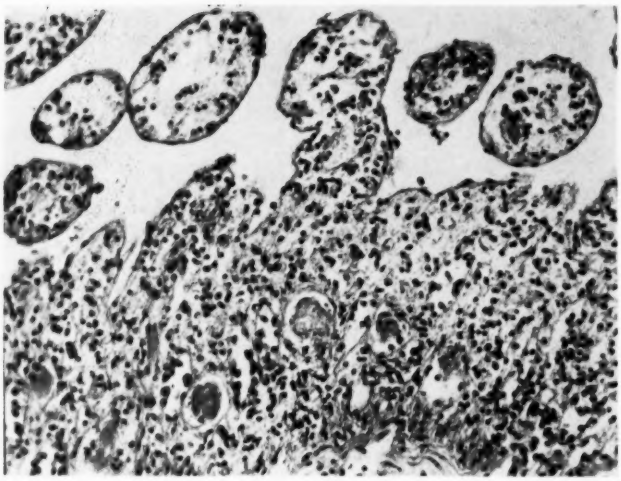


Fig. 10 (Case 1).—High-power view of mucosa of ileum, showing fibrin thrombi obstructing the lumens of the majority of capillaries. The epithelial cells have undergone necrosis and are absent from this portion of the mucosa. Hematoxylin and eosin; × 200.

After preparation with intravenous fluids, the patient was taken to the operating room and the abdomen opened. Exploration revealed a volvulus of a loop of small bowel over a postoperative adhesive band in the lower right quadrant of the abdomen. This band was released and the loop of bowel brought to the surface, where it appeared dusky blue in color. The involved loop of bowel was packed in saline for five minutes and again inspected. It was decided that the involved loop was viable. It was replaced in the abdomen and the abdomen closed.

Following this procedure the patient appeared to be somewhat better. Her blood pressure was stable at 80/40, and her pulse rate had dropped to 80 a minute. She was returned to the ward in fairly good condition at 10:30 p. m.

One hour later the nurse was suddenly unable to get a blood pressure. The apical pulse was 192 a minute. A surgeon was called. However, heroic treatment with intravenous blood and dextrose with levarterenol (Levophed) was ineffective in raising the blood pressure, and at 4:00 a. m. respiration ceased.

Autopsy.—The entire small bowel was distended and lined by a gray-green pseudomembrane. Beneath the membrane, which peeled off readily, the mucosal surface was bright red. Microscopically, the pseudomembrane was composed of fibrin, polymorphonuclear leukocytes, in various stages of degeneration, necrotic epithelial cells, and mucus (Fig. 9). The mucosa itself, as well as the submucosa, revealed numerous fibrin thrombi in the capillaries and precapillary arterioles (Fig. 10). The portion of the bowel previously the site of the volvulus was limited to a 30 cm. segment near the ileocecal valve, and microscopically all layers of this segment were necrotic. In addition to pseudomembranous enteritis, there were congestion and edema of both lungs, bilateral minimal pleural effusion, focal hepatic necrosis, and fibrous perisplenitis.

Case 2.—A 46-year-old white woman was admitted to U. S. Army Hospital, Fort Belvoir, Va., on July 12, 1954, with a diagnosis of chronic cholecystitis and cholelithiasis. On July 13 a chronically inflamed gallbladder with stones was removed. No antibiotics were prescribed. She had a completely benign postoperative course for the first two days and was taking a liquid diet well. On the evening of July 16 she had five liquid stools and vomited. She passed grossly bloody urine. Her highest temperature since surgery was 101 F. On July 17, at 7:15 a. m., she suddenly went into a severe circulatory collapse, and blood pressure was unobtainable. It was brought up into normal range only after heroic intravenous and other supportive treatment. She received large volumes of blood, plasma, serum albumin, saline, and dextrose (over 7,000 cc. in 24 hours). She passed frequent liquid stools, which contained a pseudomembrane. Stool culture showed Escherichia coli and a nonhemolytic Staphylococcus albus. There was gross blood in urine and feces. No fibrinogen level was obtained. Clotting time of the blood on July 19 was 20 minutes. She improved and maintained a normal blood pressure. Her temperature remained normal, or only slightly elevated.

She was started on erythromycin on July 19, and her intravenous supportive therapy was continued. She gradually recovered and was discharged on Aug. 3, 1954, with normal stools.

Case Apparently Due to Infection Alone

CASE 3.*—This 66-year-old white man had a surgical excision of a carcinoma of the fundus of the stomach on March 30, 1954. The tail of the pancreas and the spleen were also removed at this time. Penicillin and streptomycin were started preparatory to the operation, on March 27. One day after operation the patient became drowsy and the abdomen distended. On April 3 the temperature and pulse were elevated and he was given chlortetracycline (Aureomycin) intravenously. A stool culture revealed hemolytic Staphylococcus aureus. One day later the patient died. At postmortem examination a yellow-gray membrane was found on the intestinal mucosal surface, which extended from the duodenum to the colon. This membrane stripped off easily, leaving behind a reddish-pink surface. Hemolytic S. aureus was cultured from the intestinal contents. Microscopically no thrombi were found in the mucosa or submucosa (Fig. 11).

* Drs. Lester Frank, Francis A. Avola, and Philip Lecompte, of the Faulkner Hospital, Boston, allowed us to study and use two of their cases, which originally appeared in *Gastroenterology*.[27]

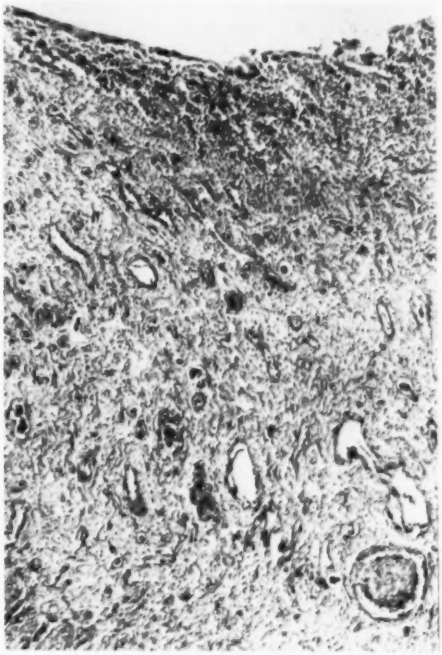
Cases Due to Intravascular Coagulation and Infection

CASE 4.*—This 67-year-old white woman had an obstructing carcinoma of the cecum, for which an ileotransversostomy was done on Feb. 14, 1953. On April 18, a right colectomy was done, with removal of a portion of the ileum. A pseudomembrane was found lining the removed portion of ileum, and culture of the membrane grew out S. aureus. The patient had been treated at home, prior to the operation, with chlortetracycline and oxytetracycline (Terramycin). The surgical incision became infected; a fecal fistula developed, and the patient died of generalized peritonitis on May 2. Postmortem examination revealed a pseudomembranous enteritis of the remainder of the small bowel, from which S. aureus was cultured. Microscopically there were numerous tumor emboli and occasional fibrin thrombi obstructing the lumens of the small vessels of the wall and mucosa of the intestine (Figs. 12 and 13).

CASE 5.—A 24-year-old white man admitted to the 97th General Hospital on July 29, 1956, and a diagnosis of acute appendicitis was made. Surgery was performed immediately, and a perforated appendix with localized peritonitis was found. He

Fig. 11 (Case 3).—Pseudomembrane on mucosal surface of ileum. No thrombi were observed in this case, and staphylococci were cultured from stool. Hematoxylin and eosin; × 50.

Fig. 12 (Case 4).—Section of ileum, showing necrosis of mucosa and multiple tiny tumor emboli and one large fibrin thrombus in submucosal vessel. Hematoxylin and eosin; × 100.



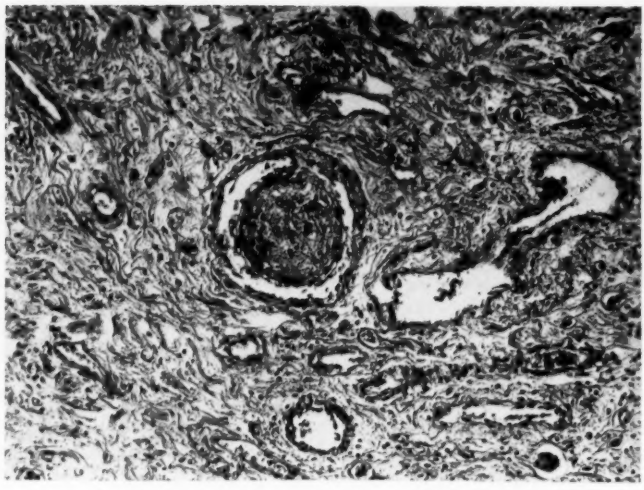


Fig. 13 (Case 4).—High-power view of thrombus in Figure 12. Hematoxylin and eosin; × 100.

was given nothing by mouth, and received penicillin, streptomycin, and oxytetracycline. The patient got along well postoperatively except for mild abdominal distention. No nasogastric suction was used. By Aug. 1 his temperature was normal, and he was taking adequate nourishment by mouth. On the evening of Aug. 2 he passed four loose stools and his temperature went up to 100 F. At 7:30 a. m. on Aug. 3 a severe circulatory collapse suddenly developed. Blood pressure and pulse were unobtainable. He vomited repeatedly and later developed a watery diarrhea. He was immediately treated for shock, including 7,850 cc. of blood and intravenous fluids, along with intravenous levarterenol. It was five hours before his blood pressure could be raised to 70 systolic. After 10 hours of intensive treatment it was up only to 100 systolic. At this point intravenous cortisone was started, and after another hour the blood pressure was up to 120/70, although the pulse was still rapid and thready. Temperature was 105 F. In the many liquid stools was a pseudomembrane. A blood fibrinogen level was 0.185 gm/100 ml. This rose to 0.334 gm. a week later. The albumin/globulin ratio, normal at first, was reversed by Aug. 10 (Table). Watery diarrhea continued until Aug. 11 and then subsided. S. aureus was isolated from the stool. In general the treatment consisted of heroic treatment for shock, followed by adequate replacement therapy for fluids, electrolytes, and protein lost. Other antibiotics were stopped and erythromycin substituted. The clinical course gradually improved. The patient developed thrombophlebitis at the site of an intravenous catheter, but by Aug. 21 he had recovered enough to go on convalescent leave.

Interpretation

The pathogenesis of the pseudomembranous enteritis in Case 1 would seem to be intravascular clotting. No antibiotics had been given, and there were no signs of infection prior to the circulatory collapse, which was sudden and spectacular. The small vessels of the mucosa and muscularis were extensively filled with fibrin thrombi. Case 2 is classified as due to intravascular clotting alone because of (1) sudden onset of severe circulatory collapse, (2) lack of previous antibiotics, (3) lack of pathogenic organisms in the stool, (4) bleeding tendency, as evidenced by bleeding from the urinary tract and gastrointestinal tract and presence of a prolonged coagulation time, and (5) lack of evidence of bacterial infection. The highest postoperative temperature was 101 F, and the temperature remained normal, or only slightly elevated, during the entire course of the enteritis. In Case 3 infection by S. aureus seems to be the most likely etiology of the lesion. In this case, antibiotics were given over a long period of time; there was a febrile course; staphylococci were cultured from the stool, and no thrombi were found in the wall of the bowel. Cases 4 and 5 seem to be examples of a combination of infection and intravascular coagulation. Both had antibiotic

Clinical Data in Case of Pseudomembranous Enterocolitis

	July			August										
	29	30	31	1	2	3	4	5	6	7	8	9	10	11	12
Temp. (highest), degrees (F)	100.4	101.8	100.4	98.8	100	105	105	104.8	101.2	100.8	102.4	99.8	101.2	100.2	99.0
Pulse (highest), per min.	88	102	100	80	95	135	148	148	120	110	130	100	100	104	96
Total fluid intake, cc.	3,000	4,800	2,620	3,640	4,040	7,850	5,220	5,605	9,030	3,950	6,235	2,800	4,175	2,650	
Total fluid output, cc.	670	3,260	2,070	860	380	5,050	4,350	5,395	6,090	3,535	4,305	2,440	3,155	3,000	
Blood Chemistry															
Serum Na, mEq/L.							137.5		138						
Serum K, mEq/L.							4.6		3.5						
Serum Cl, mEq/L.						88	100.0	79	109	111			104		
Serum CO_2, mEq/L.						14	14.0	19	25	29			29		
BUN, mg/100 ml.						35		34.4	20.6						
Fibrinogen, gm/100 ml						0.185				0.32			0.334		
Total protein, gm/100 ml.							5.00						5.70		
Albumin, gm/100 ml.							3.04						2.30		
Globulin, gm/100 ml.							1.96						3.40		
A/G ratio							1.55/1						0.68/1		
Hematology															
RBC						7,080,000									
WBC	14,850	12,050				13,500			11,600						
Platelets						396,000									
Hb, gm/100 ml.	15.2	13.4				20.4			11.6	12.8					
Hematocrit, %							60	49	38	41					

therapy, a febrile course, and S. aureus in the stool, and showed evidence of intravascular coagulation. Case 4 showed thrombi in mucosal vessels at autopsy. In Case 5 the evidence of intravascular coagulation is indirect and relies on the drop in circulating fibrinogen, from a presumed normal of 0.3 to 0.185 gm. per 100 ml. after the onset of shock. This is indicative of intravascular coagulation analogous to that seen after incompatible blood transfusion and other syndromes in man [4,5] and in animal experiments.[6-8]

Comment

The idea that ischemia is the cause of pseudomembranous enterocolitis is not new and antedates antibiotics by many years. Gesell,[25] in 1919, postulated that compensatory vasoconstriction resulting from shock reduced the blood flow to the intestinal mucosa so much that mucosal necrosis resulted.

The clinical course of pseudomembranous enterocolitis is frequently characterized by the dramatic and sudden onset of severe refractory shock which is out of proportion to the fluid loss by diarrhea into the lumen of the bowel, as noted clinically or at autopsy. This shock responds poorly to replacement therapy. It has been shown experimentally that *intravascular coagulation causes the sudden and dramatic onset of shock*,[12] and that prevention of intravascular coagulation will prevent fatal shock.[12-14] Helmer's seven "severe" cases all were characterized by the sudden onset of a severe shock that in six of the seven was fatal within 24 hours. Diarrhea was not so prominent a symptom. These cases usually follow surgery or medical or surgical shock. It has been shown [13,14] that there is hypercoagulability of the blood during the hypovolemic shock. This would tend to facilitate the formation of intravascular capillary thrombi. Also, the slowing of the blood flow through the dilated intestinal capillaries during shock would offer a fertile site for thrombus formation. Penner and Bernheim [22] postulated an ischemic necrosis of the bowel secondary to shock and arteriolar spasm as a cause of the postoperative enterocolitis. Kleckner et al.,[21] in reporting 14 cases in nonsurgical patients, again associated the disease with shock and sudden onset of profound circulatory collapse but could not find any association with antibiotic drugs or bacterial enteritis. They reported that "the use of such drugs [chemotherapeutic or antibiotic agents] cannot be implicated as a factor in the pathogenesis of pseudomembranous enterocolitis." Of the seven cases in which pseudomembranous enteritis caused a fatality, only five had any diarrhea, and in one of these diarrhea developed only sometime after onset of the circulatory collapse. The patients who did have diarrhea had a relatively mild type that ordinarily would not be fatal and could not account for the sudden onset of the profound shock. Carcinoma was the commonest diagnosis in the group. The association between carcinoma and intravascular clotting is well known.

Dearing [9] has shown that the typical clinical picture of pseudomembranous enterocolitis may exist without culturable S. aureus. Conversely, he has noted that S. aureus may exist in "pure culture" in the intestine, with the symptoms of enteritis but in the absence of a pseudomembrane. A large proportion of cases of pseudomembranous enterocolitis in the literature have had no antibiotics, and many others have not had staphylococci or any other pathogenic organism cultured from the stool.[10] Williams and Pullan [23] found no staphylococci in 6 of their 10 cases of pseudomembranous enteritis, and no antibiotic therapy was used. Dawson-Edwards and Morrissey [24] found staphylococci in only one of eight cases of acute enterocolitis following gastrectomy. Some of these had received no antibiotics. Pettet [11] found no increase in the incidence of the disease at the Mayo Clinic after the advent of antibiotic therapy. Less than half the Mayo Clinic cases had any diarrhea. It is of interest that prior to 1948 not a single case was diagnosed before autopsy, indicating that other cases were

undiagnosed. These observations cast considerable doubt on the idea that Staphylococcus infection is entirely responsible for this snydrome.

In contradistinction to these cases, the series of "mild" cases described by Helmer [3] were characterized by a 24-hour period of fever and increasing abdominal distention, followed by diarrhea. Shock was not sudden or dramatic and appeared to develop secondary to fluid loss through the gastrointestinal tract. The chinchillas described by Wood et al.[2] had a syndrome characterized by the development of diarrhea with frequent liquid or semiliquid stools, preceded by a period of lethargy (and probably fever). Later (12 to 36 hours) the animals developed shock (as evidenced by cold ears and cyanosis of the mucous membranes) and died. They all had staphylococci in their stools.

Almost all persons who have been given broad-spectrum antibiotics for a period of time develop some loose stools, and perhaps a true diarrhea. Exactly where to draw the line clinically between a severe case of this benign diarrhea and a mild case of pseudomembranous colitis may be difficult to determine. Usually the exclusive culture of staphylococci in the stool and the presence of a pseudomembrane in the feces determine the diagnosis, but there are still borderline types.

It is well known that the combination of ischemia and infection may lead to necrosis when either alone may not. If the arterial blood supply of the liver is ligated, a fatal liver necrosis may result. This is frequently prevented if infection is prevented by an antibiotic. Antibiotics are effective in preventing bowel necrosis after irradiation. Similarly, if a section of bowel is devascularized, and the bowel cut and anastomosed, the anastomosis breaks down, and death ensues.[15] However, if the same procedure is done but antibiotics are given to prevent infection, the anastomosis heals. Good effects on strangulation of the bowel are also seen as a result of antibiotics.[16,19] This may be because the infection raises the oxygen demand beyond the limited supply, thus causing tissue necrosis. Similarly, when the mucosa of the bowel has part of its blood supply cut off by vascular thrombi, a bacterial infection may result in a mucosal necrosis that would not otherwise have occurred. Contrariwise, if there is a bacterial enteritis which is then complicated by vascular thrombi, necrosis of the mucosa may result.

Conclusions

It would seem, therefore, that the syndrome of pseudomembranous enterocolitis is really the result of two separate phenomena, which may or may not overlap. Pseudomembranous enterocolitis may be classified as follows:

(*a*) A "circulatory collapse" type, caused by intravascular coagulation in the capillaries of the submucosa of the bowel, which is characterized by the sudden onset of severe refractory shock, usually occurring postoperatively. Antibiotics may or may not have been given. Diarrhea may or may not be present. The mortality is high, and is 100% if the disease is not recognized and treated vigorously. Heroic treatment for shock, with plasma, protein, and fluid therapy, is indicated.

(*b*) A "diarrhea" type, caused by a disturbance in the bacterial flora of the bowel, with predominant growth of the staphylococci and development of a staphylococcal enteritis and diarrhea. The disturbance is often associated with antibiotic therapy. It may or may not have been preceded by surgery. Staphylococci are always cultured from the stool. Shock does not occur in a sudden, dramatic moment but develops only over a period of hours or days, as a result of fluid loss into the gastrointestinal tract. Mortality in adequately treated cases is low or moderate. Treatment consists of cessation of the antibiotics, administration of a specific antistaphylococcal antibiotic, and fluid-replacement therapy.

(*c*) A combined type, initiated by a simple Staphylococcus enteritis but developing into the severe type when there is an episode

of intravascular clotting precipitated by trauma, injection of a thromboplastic agent, absorption of tissue juices, or carcinoma embolism, with intravascular clotting in the mucosal capillaries. Or, there may be a staphylococcal invasion of bowel mucosa previously damaged by intracapillary thrombi. This combination of the bacterial enteritis and capillary thrombi may actually be the commonest etiology.

Summary

It is possible to reproduce the pathology and many of the clinical manifestations of pseudomembranous enterocolitis in dogs by means of an episode of intravascular clotting in the capillaries of the bowel mucosa. It is possible to prevent this by preheparinization of the dogs.

Mucosal capillary thrombi and evidence of intravascular clotting are demonstrated in clinical cases of pseudomembranous enterocolitis.

Clinical and experimental evidence is presented to show that pseudomembranous enterocolitis is a complicated syndrome resulting from at least two causes.

(*a*) Formation of intracapillary fibrin thrombi in the submucosa and mucosa of the intestine, leading to infarct necrosis and pseudomembrane formation of the mucosa, and

(*b*) Staphylococcic infection, usually in the absence of normal intestinal flora and associated with antibiotic therapy.

Many cases may result from a combination of these two factors.

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Primary Lymphomas of the Gastrointestinal Tract

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Primary malignant tumors of lymphoid origin are not particularly common in the gastrointestinal tract. When compared with other primary malignancies, they seem rare indeed. It is estimated that of all the primary tumors of the intestinal tract, less than 3% fall into this category. It is equally true that primary involvement of the gastrointestinal tract in cases of malignant lymphoma is uncommon. Rappaport, Winter, and Hicks[7] report a survey of 253 lymphomas, only 12 of which were in the gastrointestinal tract. Gall and Mallory,[2] in 1942, reviewed 545 cases of malignant lymphoma, of which only 16 were primarily in the gastrointestinal tract.

This low incidence, however, should not discourage interest in the condition, particularly the interest of surgeons, for while it is true that most lymphomas are generalized and are best treated medically with the newer and more effective forms of radio- and chemotherapy, this is often not the case in primary lesions of the gastrointestinal tract. Here the disease tends to be unifocal and is amenable to surgical extirpation. It therefore warrants the interest and attention of surgeons. Gall and Mallory,[2] on the basis of their experience, state:

> We believe that among the malignant lymphomas there are certain cases with evidence of a single localized lesion, generally, though not always, affecting a bone or a viscus, which may be more successfully treated by radical surgery than by other means.

Marcuse and Stout,[5] in recording their observations in 13 cases of primary lymphoma of the small bowel at Presbyterian Hospital, New York, from 1932 to 1947, agree that in some instances the disease is of a focal nature and can be cured by complete excision. Three of their patients had lived 6, 8, and 14 years, respectively. In a search of the literature they found 23 cases of reported five-year cures or longer. Two patients had been treated by x-rays alone; three had received x-radiation, followed by resection, and 18 were treated by resection alone.

With regard to location, there is a great divergence of opinion as to the common sites. In the series of Gall and Mallory,[2] referred to above, 11 of the 16 tumors were in the stomach, 3 in the small intestine, and 2 in the large bowel. On the other hand, Raiford[6] reported 22 cases of lymphoblastoma of the small intestine, 21 of which were in the terminal 100 cm. of the ileum.

The most recent series was reported by Burman and van Wyk.[1] They collected 25 cases of small-intestinal and cecal lymphomas, of which 9 were lymphoblastic lymphosarcomas, 7 were reticulum-cell sarcomas, 8 were mixed lymphomas, and 1 was a giant follicular lymphoma.

There is perhaps no more confusing term in common medical usage today than "malignant lymphoma," and it may be worth while to consider what one really means by it. A lymphoma is a primary tumor of the lymph-reticuloendothelial system that does not invade the peripheral blood stream. Histogenically speaking, they are all derived from primitive reticuloendothelial cells, which may mature in various directions. Figure 1, modified from Lumb,[4] shows the histogenesis of the lymphomas.

The primitive mesenchymal cell gives rise to the primitive reticuloendothelial cell, which may, in turn, differentiate along many lines. It probably gives rise to all of the marrow and peripheral blood cells, the tis-

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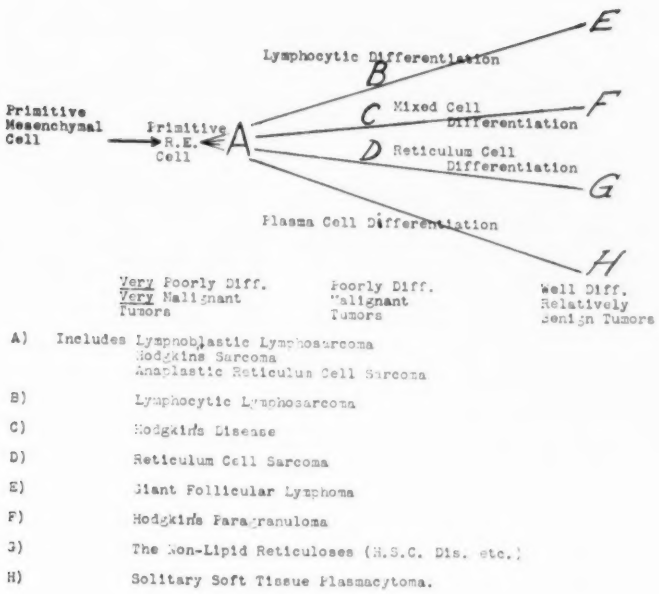

Fig. 1. — Histogenesis of the lymphomas. Modified from a diagram in "Tumors of the Lymphoid Tissue," by G. D. Lumb, by permission of the publishers, E. & S. Livingston, Edinburgh.

sue histiocytes, the lymphocytes, and the mature reticuloendothelial cells, plasma cells, mast cells, etc. Of all these many lines, we are concerned only with the four outlined in the diagram, because neoplasms arising from these cells constitute the "malignant lymphomas." Theoretically, malignant tumors may arise at any point along the course of this differentiation and maturation. We should expect those tumors arising from the more immature cells to be the more malignant, and in fact this is so. The tumors arising directly from the primitive reticuloendothelial cell just as it begins to mature are indeed very poorly differentiated, very malignant lesions. They include the following types:

A. Lymphoblastic lymphosarcoma
Hodgkin's sarcoma
Anaplastic reticulum-cell sarcoma

Histologically, these lesions may be very difficult to separate. The neoplasms arising from better-differentiated cells also behave badly but have a little better reputation than the first three. They are as follows:

B. lymphocytic lymphosarcoma
C. hodgkin's disease
D. Reticulum-cell sarcoma

The best-differentiated tumors, while potentially malignant, are reasonably well behaved. They include

E. Giant follicular lymphoma
F. Hodgkin's paragranuloma
G. The nonlipid reticuloses (histiocytosis)
H. The solitary soft-tissue plasmacytoma.

This diagram serves well to demonstrate how these different lesions are interrelated and why transition forms are so common. It is easy to understand how a giant follicular lymphoma, by dedifferentiating, may become a lymphocytic or lymphoblastic lymphosarcoma, and it is easy to see how the pathologist might have some difficulty in specifically pigeonholing a lesion differentiating in more than one direction at one time.

In selecting cases for the present series, we have included only those primary lymphomas of the gastrointestinal tract that grossly appeared to be arising within and to be limited to the gastrointestinal wall itself. We have deliberately eliminated all cases in which the disease appeared to be multicentric, in which there was involvement of distal mesenteric or para-aortic

TABLE 1.—*Cell Type*

Reticulum-cell sarcoma	8
Hodgkin's disease (granuloma)	5
Plasmacytoma	1
Giant follicular lymphoma	1
Total	15

TABLE 2.—*Location*

	Reticulum-Cell Sarcoma	Hodgkin's Disease	Plasmacytoma	Giant Follicular Lymphoma
Pylorus	1			
Jejunum	1	2 *		
Upper ileum	1		1	
Terminal ileum	1	1 *		
"Small bowel"		1		
Cecum	3			
Ascending colon		1		
Transverse colon		1		
Rectum	1			1

* One case of Hodgkin's disease apparently had two primary lesions—one in the jejunum and one in the terminal ileum.

nodes, or in which there was a leukemic phase. In other words, we have included only those cases in which at the time of the original examination the neoplasm was theoretically resectable. A search of the hospital records since 1950 disclosed 15 cases in which enough data were available for analysis. The purpose of this paper is to review these 15 cases as to the nature of the pathological lesion, its location, the presenting signs and symptoms, the surgical treatment, and the eventual outcome.

With regard to the pathological nature of the tumors, reticulum-cell sarcoma and Hodgkin's granuloma were by far the commonest (Table 1). It is unusual that not a single case of lymphoblastic or lymphocytic lymphosarcoma could be included in the series. In all our lymphosarcomas the primary lesion appeared to be in the mesenteric lymph nodes, with only secondary involvement in the intestine itself.

There were only one lymphoma of the stomach, seven of the small bowel, and seven of the large bowel and rectum (Table 2).

It is seen that only two of the lymphomas occur in the terminal ileum, in contrast to 21 of Raiford's[6] 22 cases. One case of Hodgkin's disease had what appeared to be two primary lesions, one in the jejunum and one in the terminal ileum (Figs. 2 and 3).

The most frequent symptom (Table 3) was pain, occurring in 13 cases. This was nearly always an intermittent, crampy type of pain, caused by intermittent partial small-bowel obstruction. One acute perforation occurred in a reticulum-cell sarcoma of the terminal ileum. This was in a 67-year-old man whose only previous symptom had been anemia and occult blood in the stool. Six months previously he had been studied, and a very large benign rectal polyp had been discovered and removed by fulguration. The lesion of the terminal ileum had not shown in barium series (Figs. 4 and 5). The other acute perforation occurred in one of the two cases of Hodgkin's disease of the

Fig. 2.—Hodgkin's disease involving both the jejunum and the terminal ileum.

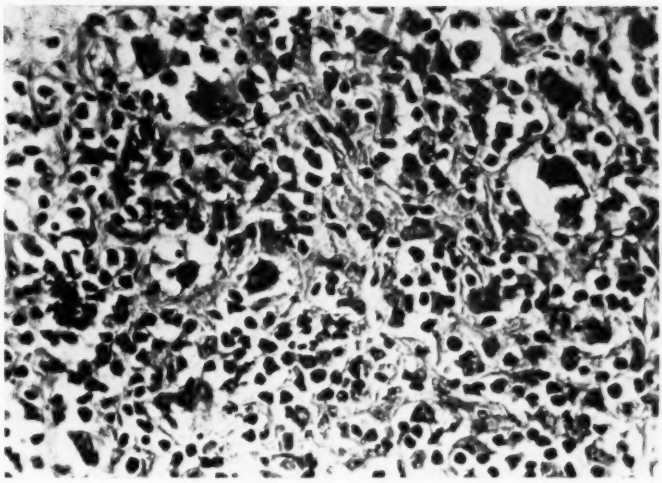

Fig. 3.—Hodgkin's disease of the jejunum. Enlarged from × 600.

TABLE 3.—*Presenting Signs and Symptoms*

Palpable mass, abdomen	4
Palpable mass, rectal	2
Gross melena	3
Weight loss	6
Acute perforation	2
Constipation	3
Diarrhea	2
Partial obstruction	9
Complete obstruction	0
Pain	13

jejunum. This 68-year-old man also had several large gastrointestinal hemorrhages during a six-week period prior to his perforation. Both patients died without surgery, and the presence of the tumor was proved at autopsy. There is no record of examination for occult blood, but two cases showed gross blood in the stool, i. e., tarry stool. None of the small-bowel tumors were diagnosed by barium meal. All patients had routine upper gastrointestinal series, but in no case had a serial small-bowel follow-up study been requested.

The plasmacytoma deserves special mention. Hampton and Gandy[3] recently reported an interesting case occurring in the gastrointestinal tract and reviewed the literature. They found only 21 cases previously reported as occurring primarily in the gastro-intestinal tract. The case reported here is the 23d case, that of a 27-year-old white man, who had suffered from intermittent pain, nausea, and vomiting for approximately one year. There was a trans-

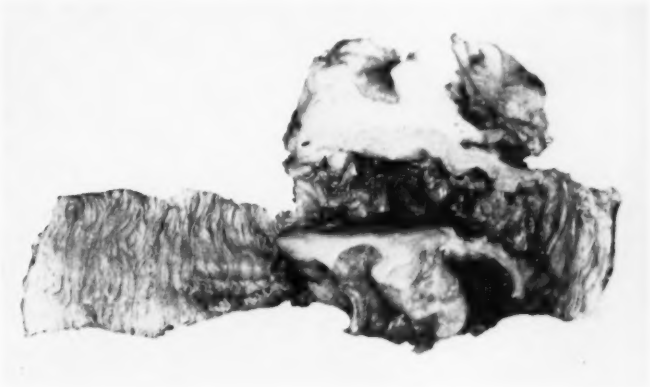

Fig. 4.—Reticulum-cell sarcoma of terminal ileum.

Fig. 5.—Reticulum-cell sarcoma of terminal ileum. Reticulum stain; enlarged from × 600.

Fig. 6.—Plasmacytoma of upper ileum, showing sheets of plasma cells, which comprised the bulk of the tumor. Enlarged from × 600.

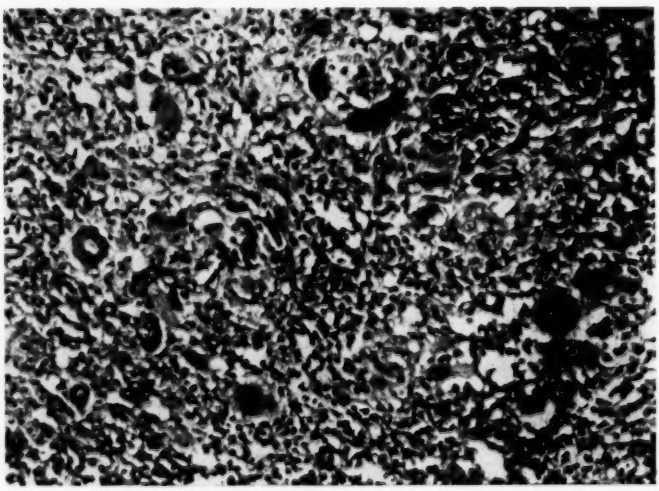

Fig. 7.—Focal areas of amyloid deposition and giant-cell reaction in plasmacytoma. Enlarged from × 600.

TABLE 4.—*Age and Sex Incidence*

Sex Incidence		Age of Onset, Decade					
		3	4	5	6	7	8
Men 6	Cases	1	0	2	3	4	5
Women 9							

verse plaque in the lower jejunum 2 cm. in width and involving three-fourths of the bowel circumference. The patient died five weeks later of peritonitis following an intussusception of the anastomosis (Figs. 6 and 7).

Table 4 gives the sex and age incidence. This series is too small for these figures to be significant.

Table 5 outlines the treatment received, and Table 6 presents the follow-up. In one case, the reticulum-cell sarcoma of the pylorus was bypassed as a palliative measure. The two previously mentioned cases of perforation and hemorrhage with perforation were treated by supportive measures. The case of giant follicular lymphoma of the rectum was not traceable. In all other cases the tumor was resected, and only one patient received deep x-ray therapy following resection. Only 1 of our 15 patients has survived five years (Table 6).

Conclusions

Primary lymphomas of the gastrointestinal tract are uncommon tumors.

Although the prognosis is generally poor, it is not hopeless, and there is reason to believe that more of these lesions than is realized may be resectable.

TABLE 5.—*Treatment (14 Cases)*

Location	Resection	Bypass	Supportive	Resection and Deep X-Ray
Pylorus		1		
Jejunum	2 *		1	1
"Small bowel"	1			
Upper ileum	1			
Terminal ileum	1 *		1	
Cecum	3			
Ascending colon	1			
Transverse colon	1			
Rectum	1			

TABLE 6.—*Follow-Up*

Deceased Patients				
From First Symptom Until Death				
0-1 Mo.	1-6 Mo.	6 Mo.-1 Yr.	1-3 Yr.	6-8 Yr.
1	2	4	1	1

Surviving Patients		
Period of Observation		
5 or More Yr.	1-5 Yr.	Less than 1 Yr.
1 (13 yr.)	3 *	1

* One patient now suffering a recurrence.

Perhaps an awareness of the condition could lead to earlier diagnosis and earlier resection, with more possible cures. Although all six of the patients with small-bowel lymphomas complained of intermittent, crampy abdominal pain, no serial films were made. Barium swallow or barium enema revealed all the lymphomas reported in the pylorus and large bowel, but the preoperative diagnosis in all cases was carcinoma. This misdiagnosis may be an academic point but possibly results in earlier resection.

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Physiological Approach to Successful Treatment of Endotoxin Shock in the Experimental Animal

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Introduction

The gravity of Gram-negative bacteremia has long been recognized,[1,2] but it is only recently that the lethal effect of these organisms when present in the systemic circulation has been correlated with their ability to produce shock.[3] The ability to cause shock in man, as well as in a variety of laboratory animals, is apparently dependent upon a lipoprotein-carbohydrate complex, or endotoxin, which is liberated at death from the cell wall of the Gram-negative bacteria.[4] While the mechanism by which endotoxin causes shock is not clear, there is increasing evidence that its faculty of causing profound vasospasm in the small blood vessels[5,6] is intimately linked with its capacity to cause shock. In the dog, hemoconcentration, plasma loss, increased plasma hemoglobin, bloody diarrhea, and hemorrhagic necrosis of the bowel mucosa regularly follow the injection of endotoxin and are apparently the result of the vasospastic effect of endotoxin on the small blood vessels of the bowel.[7] These findings are similar to those previously found in dogs dying of irreversible shock following prolonged hemorrhage.[8,9]

In the present study we have standardized endotoxin shock in the dog and then compared the effects of drugs (chlorpromazine and phenoxybenzamine hydrochloride [Dibenzyline]) which would counteract a vasospastic effect of endotoxin with the effect of drugs (norepinephrine,* metaraminol,† and hydrocortisone) which currently form the basis for the clinical treatment of shock due to Gram-negative bacteria. In addition, because of evidence obtained in the endotoxin experiments which suggested that hydrocortisone in large doses acted as an adrenergic-blocking agent, the effect of hydrocortisone on epinephrine shock in the dog was also studied.

Materials and Methods

In all experiments, adult mongrel dogs of either sex were used and were placed under sedation with morphine sulfate, 2 mg/kg., 30 to 60 minutes prior to an experiment. A femoral artery was cannulated for continuous monitoring of blood pressure, and both femoral veins were cannulated for the taking of blood specimens and the injection of medications. Prior to inducing shock, the plasma volume of all dogs was measured using a micromethod utilizing Evans blue (T-1824), the injected dye being weighed and the plasma analyzed in microcuvettes in a Beckman DU Spectrophotometer.[10] The hematocrit and plasma hemoglobin[11] were also determined at this time.

Endotoxin shock was induced by injecting intravenously 7.5 mg/kg. of a crude endotoxin prepared from killed Escherichia coli cells by a method previously described.[12] This dose of endotoxin was lethal to 90% of dogs. Epinephrine shock was induced by adding 2 mg/kg. of epinephrine, 1:1,000 solution,‡ to 120 ml. of isotonic

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U. S. Public Health Service Postdoctoral Research Fellow in Arthritis and Metabolic Diseases (Dr. Lillehei). The John and Mary R. Markle Scholar in the Medical Sciences (Dr. MacLean).

* Winthrop Laboratories.

† Sharp & Dohme.

‡ Parke, Davis & Company.

TABLE 1.—*Endotoxin Shock* *

Group	No. Dogs	No. Survivors	Duration Survival, Hr.	Hematocrit Increase, %	Plasma Loss, %	Plasma Hemoglobin Increase, Mg., %
Controls	36	3	12.1±6.1	33.6±13	36.6±11.7	84.5±20
Chlorpromazine	10	6	--	12.1±5.0	10.3±6.1	28.0±14
Phenoxybenzamine	10	9	--	6.70±3.8	6.72±8.2	28.2±15
Norepinephrine (Levophed)	10	0	10.2±5.2	29.7±12	34.7±14	144±58
Metaraminol (Aramine)	10	0	5.10±2.8	31.5±9.1	40.4±8.5	193±83
Sublethal endotoxin and metaraminol	5	0	15.8±6.1	27.0±7.7	34.9±13.1	113±34
Hydrocortisone	10	9	--	7.91±3.5	4.06±3.7	33.2±13

* Mean values with standard deviations.

saline and administering this solution at a rate of 16μg. to 17μg/kg/min. for 120 minutes.[13] To minimize the cardiac arrhythmias caused by epinephrine, atropine sulfate,§ 0.2 mg/kg., was administered to the dogs prior to starting the epinephrine drip.[13] This dose of epinephrine was lethal to 90% of adult dogs.

At 90-minute intervals following the induction of endotoxin or epinephrine shock, the hematocrit, plasma hemoglobin, and plasma volume were determined for periods up to eight hours. When the mean arterial blood pressure (MABP) of the dog was below 90 mm. Hg, samples of blood for analysis for Evans blue were taken at 15- and 20-minute intervals following the injection of the dye, rather than at the usual 10- and 15-minute intervals.

Experimental Observations

Results in endotoxin experiments are summarized in Table 1. Values for hematocrit increase, plasma hemoglobin increase, and plasma loss are maximums occurring in the first eight hours.

Controls.—Within one minute following the injection of endotoxin the MABP fell precipitously to shock levels, 40 to 60 mm. Hg, but returned to normal levels within five minutes. Within 60 to 90 minutes later, a secondary, more gradual fall in MABP began, and the pressure continued to fall until death occurred, in most cases within 12 hours (Fig. 1). Coincident with the gradual fall in MABP, significant plasma losses were measured along with a parallel hemoconcentration. These losses usually increased until death occurred. Plasma hemoglobin also increased. Bloody diarrhea often accompanied the secondary blood pressure fall. At autopsy, hemorrhagic necrosis of the bowel mucosa was the most prominent finding (Fig. 2), although liver congestion, tubular damage in the kidneys, and subendothelial hemorrhages in the left ventricle of the heart were also present.

Effects of Adrenergic Blocking Agents.—Ten dogs were given chlorpromazine, 25 to 50 mg/kg., intramuscularly, 30 to 60 minutes prior to receiving endotoxin. This amount of chlorpromazine reduced the MABP from the usual 120 to 140 mm. Hg to 100 to 110 mm. Hg and markedly depressed the dog's sensorium. Following the injection of endotoxin, these dogs had an immediate fall in MABP with recovery, but

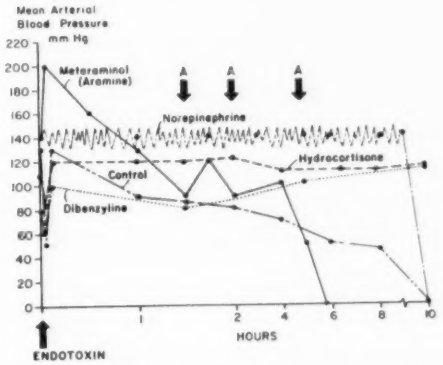

Fig. 1.—Mean arterial blood pressure response in typical endotoxin shock experiments. *A* indicates where metaraminol was administered after the initial dose to maintain blood pressure.

§ Eli Lilly & Company.

Fig. 2.—Typical microscopic section of hemorrhagic mucosal necrosis in the small bowel in a control dog given a lethal dose of endotoxin. × 60.

only a moderate fall 60 to 90 minutes later. By four to six hours later, these dogs had regained a normal blood pressure. Plasma losses and hemoconcentration were minimal in these dogs, and plasma hemoglobin rose only moderately in the first eight hours. Bloody diarrhea did not occur. Six of the dogs lived 72 hours or longer and were considered permanent survivors. When killed, these survivors showed only moderate liver congestion and tubular damage in the kidneys. The bowel was normal (Fig. 3).

Ten dogs given 0.5 mg/kg. of phenoxybenzamine hydrochloride intravenously 60 minutes before endotoxin was injected followed a course similar to that described for chlorpromazine-treated dogs, except that these dogs did not exhibit the depression of the central nervous system seen in chlorpromazine-treated dogs. Plasma losses, hemoconcentration, and plasma hemoglobin increases in these phenoxybenzamine-treated dogs were significantly less than those seen in controls. Nine of the dogs were permanent survivors and at autopsy exhibited findings similar to those described above for chlorpromazine-treated dogs.

Effects of Vasopressor Agents.—Norepinephrine: In 10 dogs variations in blood pressure following endotoxin injection were prevented by starting an intravenous drip of norepinephrine, 16 to 32 mg. of levarterenol (Levophed) base in 500 ml. of 5% dextrose, simultaneously with the endotoxin injection. By this means, the MABP was supported at 120 to 140 mm. Hg for as long as the animal remained responsive to the effects of the norepinephrine.

Despite this support, these dogs did not differ significantly from controls in plasma loss, hemoconcentration, or survival time. In addition, plasma hemoglobin levels rose to extremely high levels before death. At autopsy extensive bowel, and even liver, necrosis was found. The kidneys showed

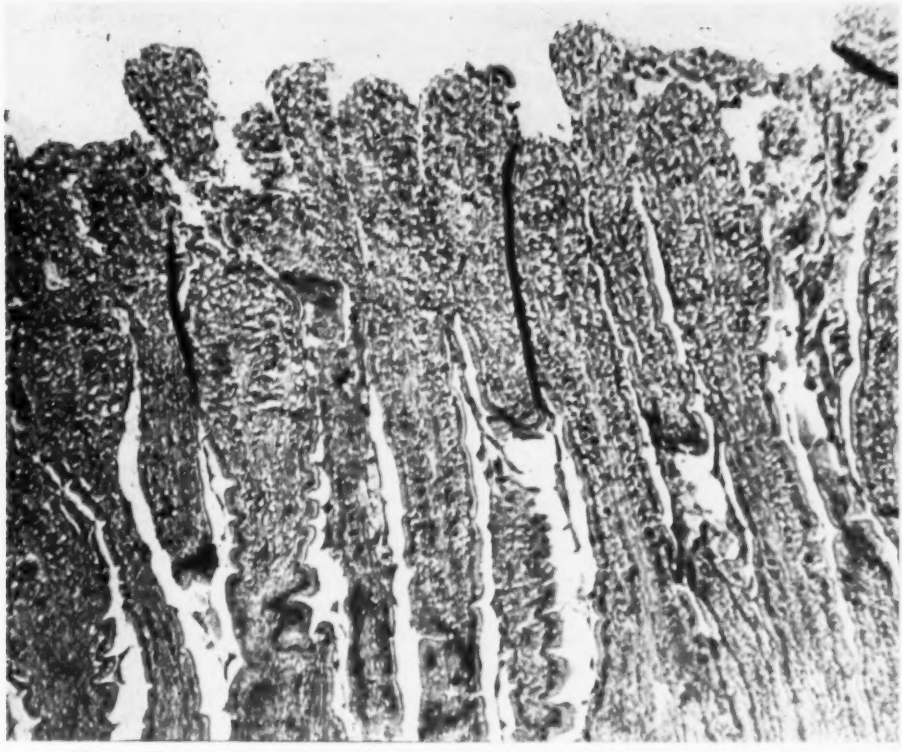

Fig. 3.—Typical microscopic section of small bowel showing normal mucosal architecture in a chlorpromazine-treated dog given a lethal dose of endotoxin. Reduced to 58% of mag. × 100. This dog was killed 72 hours following the experiment.

marked tubular damage, and subendothelial hemorrhages covered the surface of the left ventricle.

Metaraminol (Aramine): Ten dogs in this group were given intravenous metaraminol bitartrate, 0.5 to 1 mg., simultaneously with the injection of endotoxin. This prevented the initial blood pressure fall. When the MABP later fell below 90 mm. Hg, this dose of metaraminol was repeated. This procedure was continued for as long as the dog remained responsive to the vasopressor effects of metaraminol. The total amount of metaraminol used in these experiments never exceeded an amount, 1 mg/kg., previously found to be well tolerated by all normal dogs. The combination of endotoxin and metaraminol halved the mean survival time of dogs treated in this manner, and all died. Plasma losses and hematocrit increases were large, and plasma hemoglobin rose to the highest levels recorded for any of the endotoxin experiments in this study. At autopsy, edema, hemorrhage, and necrosis in the bowel were especially striking, as were the congestive changes in the liver and kidneys and the subendothelial hemorrhages in the left ventricle of the heart.

Potentiation of Sublethal Endotoxin Shock.—Because of the apparent synergistic effect of endotoxin and metaraminol noted in the previous experiments, five dogs were given a dose of endotoxin, 1 to 1.5 mg/kg., which we had previously found to cause death in less than 20% of adult dogs. Ten minutes before the endotoxin was injected, these dogs were given a single intramuscular dose of metaraminol bitratrate, 0.5 mg/kg. This combination of sublethal endotoxin and metaraminol proved lethal for all five

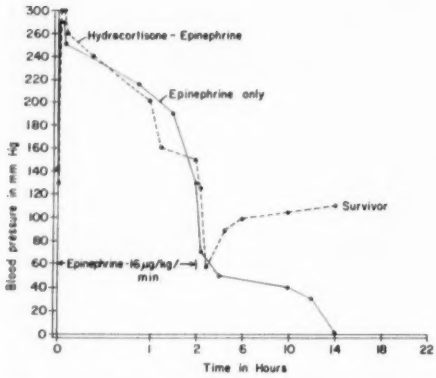

Fig. 4.—Mean arterial blood pressure response in typical epinephrine shock experiments.

dogs, and the characteristic plasma findings of lethal endotoxin shock were measured. The autopsy findings in these dogs also differed in no way from those described in control dogs given a lethal dose of endotoxin.

Effects of Hydrocortisone.—Ten dogs were given hydrocortisone, 15 mg/kg., intramuscularly daily for four days. On the fifth day they received endotoxin. The reactions of dogs in this group to endotoxin differed distinctly from those observed in all other groups of dogs in this study. While there was an initial drop in MABP, it rarely fell below 100 mm. Hg, and recovery was rapid. Following this the MABP remained at normal levels throughout the course of the experiment, and nine of the dogs were permanent survivors. Plasma volume and hematocrits did not change significantly from preendotoxin levels. Plasma hemoglobin rose only moderately in the first eight hours and returned to normal levels by the following day. At the time of killing, the liver was congested, and some tubular damage could be seen in the kidneys of these dogs, but the bowel was normal.

Effects of Hydrocortisone in Epinephrine Shock.—The beneficial results obtained with hydrocortisone in endotoxin experiments suggested that, in large doses, hydrocortisone was acting as an adrenergic-blocking agent. For this reason, we studied the effect of hydrocortisone on lethal epinephrine shock.

Controls: Epinephrine shock was induced in 10 dogs in the manner described above, and this proved lethal to 9 of the 10 dogs. Figure 4 illustrates a typical experiment. The plasma losses, hematocrit, and plasma hemoglobin increases measured in these dogs closely paralleled findings in endotoxin shock described above (Table 2). Autopsy findings were also similar to those seen in dogs dying of endotoxin shock. The liver was congested; there were tubular lesions in the kidneys, and the heart showed extensive subendothelial hemorrhages in the left ventricle. The bowel was edematous, with scattered hemorrhagic lesions in the mucosa.

Hydrocortisone Pretreatment: When epinephrine shock was induced in 10 dogs pretreated with hydrocortisone, 15 mg/kg., for four days prior to the experiment, 8 of the dogs survived permanently. Although mean plasma losses and plasma hemoglobin increases were less in these dogs than in the epinephrine-shock, control dogs, the differences were of only doubtful significance. Nevertheless, hydrocortisone in some way protected the dogs against the pernicious effects of prolonged epinephrine stimulation. When these surviving dogs were killed,

TABLE 2.—*Epinephrine Shock* *

Group	No. Dogs	No. Survivors	Duration Survival, Hr.	Hematocrit Increase, %	Plasma Loss, %	Plasma Hemoglobin Increase, Mg., %
Controls	10	1	19.9±16	29.7±9.3	40.4±9.9	161±64
Hydrocortisone	10	8	--	25.3±12	29.7±11	119±56

* Mean values with standard deviations.

autopsy revealed liver congestion and occasional tubular damage in the kidneys, as well as subendothelial hemorrhages in the left ventricle of the heart. The bowel usually appeared normal.

Comment

The results of these experiments indicate that endotoxin exerts a violent effect on the blood vessels of the dog, destroys their integrity, and causes critical ischemia in the bowel and other organs. This course of events terminates in hemorrhagic necrosis in the bowel, with resultant plasma losses and increased plasma hemoglobin. While plasma losses are large, these losses alone are not directly the cause of death, since replacement of such losses is of only temporary benefit.[7] Rather, the plasma loss is apparently an indicator of the peripheral ischemia resulting from the vasospastic effects of endotoxin. The extent of plasma loss in clinical cases of endotoxin shock is uncertain. Ebert and Stead (1941)[14] reported no significant plasma loss in eight patients with circulatory failure due to acute infections; however, it is worth recalling that all of the patients in this series apparently had Gram-positive bacteremia. Further clinical studies are needed to determine the extent of plasma losses resulting from Gram-negative bacterial shock.

The ability of adrenergic-blocking agents to lessen or prevent the deleterious effects of endotoxin has previously been demonstrated in mice[15,16] and rabbits,[17] with doses of chlorpromazine or phenoxybenzamine similar to those used in these experiments. But, while endotoxin apparently has a sympathomimetic effect and can be reversed with adrenergic-blocking agents, there is no evidence that endotoxin shock results from or causes hyperactivity of the sympathetic nervous system or hypersecretion of the adrenal medulla, even though the physiological and pathological resemblances between endotoxin and epinephrine shock are striking. Indeed, recent experiments in our laboratory indicate that total sympathectomy does not protect animals from the lethal effects of endotoxin.

Vasopressor agents have recently been under fire because of the increased incidence of liver necrosis seen at autopsy in patients receiving one of these agents shortly before death.[18] Similarly, in the present study, there was evidence of increased tissue damage in animals receiving a vasopressor agent. While norepinephrine treatment did not influence survival time adversely when compared with controls, the combination of endotoxin and metaraminol was especially onerous. The synergistic effect of metaraminol and endotoxin was further revealed by the ability of metaraminol to potentiate the effects of a sublethal dose of endotoxin and cause death in 100% of dogs. A similar relationship between endotoxin and epinephrine has recently been demonstrated by Thomas in the rabbit.[19]

There is no doubt that any of the various vasopressor agents increase, at least temporarily, venous return, cardiac output, and systemic blood pressure during endotoxin shock, but laboratory data demonstrating this ability have been derived from brief observations immediately following their administration, and no observations over a prolonged period have been made.[20] The promiscuous and prolonged use of such agents in a condition already aggravated by excessive vasospasm appears illogical, since increased tissue ischemia and damage is a probable result.

The ability of hydrocortisone to protect the dog against excessive vascular tone present in both endotoxin and epinephrine shock is provocative. The effect is apparently pharmacological rather than physiological because of the large amount of hydrocortisone required. In this connection, the failure of investigators both in the laboratory[21] and clinically[22] to establish definitely the place of hydrocortisone in the treatment of Gram-negative bacterial shock may be a result of administering inadequate amounts, with the result that the desired pharmacological effect is not realized, for

there is little evidence in man or the dog that, except in rare circumstances, adrenal insufficiency or exhaustion ever occurs, even under the severest and most prolonged stress.[23]

Finally, we must state clearly that we advocate no sweeping changes in the clinical therapy of shock due to Gram-negative bacterial endotoxins on the basis of these laboratory results. However, the continuing high mortality rate following Gram-negative bacteremic shock,[3,24,25] which has not improved markedly in the past 50 years,[2] should cause us continually to reappraise our present methods of treatment in the light of our increasing knowledge of the physiological disturbances caused by endotoxins.

Summary

The course of endotoxin shock in the dog was not benefited by support of blood pressure with norepinephrine or metaraminol (Aramine). Moreover, metaraminol actually potentiated the shock due to the endotoxin of E. coli bacteria. Adrenergic-blocking agents, chlorpromazine, or phenoxybenzamine (Dibenzyline), increased the number of survivors from endotoxin shock by blocking vasospastic effects of endotoxin. Hydrocortisone, in pharmacological amounts, also increased survival from endotoxin shock, and this was also apparently due to its ability to protect the dog against the vasospastic effects of endotoxin.

Miss Betty J. Newman, B.S., and Mr. Donald E. Battles assisted in the performance of these experiments. Drs. G. M. Bradley and W. W. Spink, of the Department of Medicine, University of Minnesota Medical School, supplied us with the endotoxin used in these experiments. The Upjohn Company supplied us with hydrocortisone (Solu-Cortef), and Smith, Kline, and French Company supplied us with chlorpromazine (Thorazine) and phenoxybenzamine (Dibenzyline).

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When Should Proximal Colostomy Be Performed for Gastrojejunocolic Fistula?

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Gastrojejunocolic fistula in the majority of cases is a complication of inadequate surgery for peptic ulceration. Its history is the history of peptic ulcer surgery. In 1881 the first anterior gastrojejunostomy was performed by Wolfler. In 1885 the first posterior gastrojejunostomy was done. This was carried out by von Hacker. As soon after this as 1889, the first stomal ulcer was reported by Braun, and by 1902 the succession of complications of recurrent ulcer was complete. In that year Czerny closed the first gastrocolic fistula. Since then this surgical disease has come to be well recognized, and excellent reviews have appeared.[1,2]

The principles in the management of these cases are now generally agreed upon. They are, namely, to diagnose the fistula early, to close it as soon as the patient is fit, and to prevent its recurrence by adequate surgery designed to reduce the acidity. For patients who are in good condition a one-stage operation is generally preferred. The fistula, and associated bowel, are resected, and a subtotal gastrectomy with or without vagotomy is carried out. For those in poor condition the consensus is that a proximal colostomy, as advocated by Pfeiffer,[3] will, by the relief of diarrhea, enable the patient to recover sufficiently to withstand the major resection. There would be little point in recording yet another series of gastrojejunocolic fistulae but for the fact that local experience has led us to question the value of proximal colostomy in certain cases, and to suspect that the actual site of the fistula determined the result of proximal colostomy.

In the past 21 years, 21 patients, with 24 separate fistulae, resulting from peptic ulcer, appear in the records of Shaughnessy Hospital, Vancouver, and the Vancouver General Hospital. All patients have been traced. As early diagnosis is the key to successful treatment, the symptomatology was reviewed. When the cases in which proximal colostomy was carried out were evaluated, it became apparent that the site of the fistula was the important factor in the success or failure of proximal colostomy to afford relief. Those patients who had a jejunocolic fistula were benefited; those with a gastrocolic fistula were not.

The conduct of these cases has spanned the evolution of the principles of treatment already stated, and it provides evidence in support of those principles.

When it became apparent that the site of the fistula was of importance, because of the small number of gastrocolic cases which occur (for recurrent ulcer is less common in the stomach than at the stoma or in the loop of anastomosed small bowel), five cases of gastrocolic and one of jejunocolic fistula due to carcinoma were obtained. Because this is a different disease process, these cases have been reviewed separately, but they do support the main contention that the site of the fistula is of importance.

Of the 24 cases due to peptic ulceration, 1 has not been included in the main analysis. In this case the fistula was a result of trauma, a fall across a boat-launching roller. The colon was torn away from the adhesions at the site of the gastrojejunal anastomosis, producing a gastrojejunocolic fistula, and also peritonitis. The patient was oper-

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ated on the same day, by simple closure of the openings, remained well for three years, and was then lost to follow-up.

Analysis of Case Material

Of the remaining 23 cases of fistula, all had had posterior gastrojejunal anastomosis, but only 3, in addition, had had partial gastric resection. The previous pathology had been duodenal ulcer, in 13 cases, and gastric ulcer, in 3 cases, and was not known in 4 cases. Three fistulae were recurrent. The operation had been done on the average 10 years earlier, the shortest period being 5 months and the longest 26 years, with the remainder of the cases fairly evenly distributed between these two extremes.

There was only one woman among these cases. Though she had a recurrent fistula, the symptoms and signs did not differ, and her case will not be differentiated further.

The average age at onset was 56; the youngest patient was 28, and the oldest was 80, but his fistula was discovered only at autopsy. The oldest patient with symptoms was 77. The greatest number of patients were in the sixth or seventh decade of life. This is a rather older age incidence than is usually reported.

Symptomatology

No history could be obtained from the patient whose fistula was found at autopsy. Of the remaining 22 fistulae, the presenting symptom in all was diarrhea (Table 1). In three cases the attacks were intermittent, and in two the diarrhea occurred suddenly while the patient was in hospital for another condition. The other patients had all had diarrhea for periods up to nine months at the longest. Nocturnal diarrhea was not a constant feature. In eight cases of fistula the diarrhea was more frequent at night; in two, more frequent by day, and in five, the day and night frequencies were equal. In six cases no comment was made; presumably there was equal frequency. The stools were usually described as being pale, watery, and in some cases as containing undigested food. An occult-blood examination was negative in seven out of eight patients examined.

TABLE 1.—*Symptoms in Twenty-Two Fistulae*

Diarrhea		22
Weight loss		22
Vomiting		12
Vomiting, fecal		5
Foul eructations		10
Pain with fistula		10
Appetite	Poor	6
	Good	5

Twelve patients had vomiting; in five it was described as fecal, and in the remainder it consisted of partly digested food. Ten had foul eructations, one likening it to "the smell of an exhumed body from a graveyard." Ten had pain while the fistula was present; three had no pain at any time, and in two the pain disappeared with the appearance of the fistula. The pain was felt in the epigastrium in eight, on the right side in three, and in the left lower quadrant in one. In four it occurred after eating. Seven patients had tenderness, usually epigastric, but in two it was in the right lower quadrant. The remainder had no tenderness. No masses were palpable in any of the patients. All had lost weight—30 lb. on the average. Four patients were noted to be in normal nutrition; five had poor nutrition, and eight were emaciated. Six had poor appetites; five had good appetites. Acid-level determinations were carried out in nine patients. None had achlorhydria, and in only one was the level low. Other laboratory findings were not remarkable. The majority of patients showed moderate anemia, of a normochromic, normocytic type. Macrocytosis was not seen. A moderate leukocytosis was seen, but only three patients had counts over 10,000 cells per cubic millimeter. The differential count was normal. Serum proteins, when estimated, were within normal limits, with a normal albumin/globulin ratio. Electrolytes were determined only in the later cases, and were not grossly abnormal. However, most patients were hypotensive, and this may reflect

a degree of hypovolemia of electrolyte and fluid imbalance.

X-Ray Findings (Table 2)

Of the 23 cases of fistula, records are available on barium-enema examinations in 19. In all a fistula was demonstrated. The records were not present in two cases, and in one the examination carried out was obscure. The patient whose fistula was discovered at autopsy had had no x-ray examination. The usual sequence is for the barium to pass up the descending colon to the splenic flexure and to pass into the distal transverse colon. Suddenly barium appears in a loop of small bowel, and from there it fills other loops; and some passes into the stomach either directly or by the gastrojejunostomy.

TABLE 2.—*Radiological Examination*

	Patients Examined	Fistula Demonstrated	Site of Fistula Demonstrated		
			Gastrocolic	Jejunocolic	Gastrojejunocolic
Barium enema	19	19	3	11	5
Barium meal	17	3	2	1 (?)	Nil

Seventeen patients had a barium meal. Of these, the radiologist reported a fistula present in only three. As will be discussed later, two of these had gastrocolic fistulae. Some of the films were available for review; and in an additional four films a small amount of barium could be seen in a loop of bowel which had the configuration of large bowel, though this was not certain, nor did the radiologist comment on it at the time.

Methods and Results of Treatment (Table 3)

Three patients had no operation. The remainder were subjected to various procedures.

Two patients had a simple take-down of the fistula and anastomosis, with repair of the openings. These patients were in poor shape, and they both died.

Four patients had repair of the fistula, the old stoma being left or a new gastroenterostomy made. They all survived operation. Three had recurrent fistulae, and the fourth died of a coronary thrombosis 14 months after operation. At autopsy he was shown to have a penetrating recurrent ulcer, 2 cm. in diameter, just distal to the stoma, in the efferent loop of jejunum.

TABLE 3.—*Methods and Results of Treatment in Nineteen Cases*

Method	No. of Patients	Results	
Simple take-down of fistula and anastomosis	2	Operative death,	2
Repair of fistula with gastroenterostomy	4	Recurrent fistula	3
		Recurrent ulcer	1
Single-stage repair with partial gastrectomy	9	Operative death	1
		Recurrent ulcer	1
		Recovery	7
Two-stage operation, proximal colostomy, with subsequent gastrectomy	5	Operative death	1
		Recurrent ulcer	1
		Well	3

Nine had a single-stage repair with partial gastrectomy, or the original gastrectomy was left. One died. He had a carcinoma of the ascending colon and had had in addition to resection of the fistula, a right hemicolectomy. The other eight survived operation. One subsequently died of drowning, without further ulceration; one has a high ulcer of the lesser curvature of the stomach (he had had a gastroduodenal anastomosis); the other six are well.

Following the suggestion that in poor-risk patients who are dehydrated, hypochloremic and hypokalemic from continual vomiting and diarrhea, starved, and emaciated a two-stage operation should be done, the first stage being a proximal colostomy, five patients were so treated. They are of especial interest. These patients all had a proximal colostomy with subsequent partial gastrectomy, or the original gastrectomy was left. One died after the second stage, of peritonitis at the site of the colostomy. Four now remain well, though one had recurrent ulcer with perforation and required further gastric resection and vagotomy. Of these five patients, two had relief from the

proximal colostomy, in one dramatic, with immediate cessation of diarrhea and vomiting. Two had no relief from the colostomy, and one had equivocal relief, continuing to have diarrhea. The patients who had relief had jejunocolic fistulae, and of the two who had no relief, one had a frank gastrocolic fistula, and the other a gastrojejunocolic fistula, the fistula being at the stoma and involving predominantly the stomach.

Of the seven patients who died while in hospital, three died without operation, one being considered too ill, one being without diagnosis and symptomless, and one dying of sudden adrenal apoplexy during investigation. Of the other four deaths, the cause was unrecorded in one, but was probably due to electrolyte imbalance five days after an emergency gastroenterostomy, which had been carried out for pyloric obstruction after the fistula had been closed and the original gastroenterostomy undone. In another, small-bowel obstruction occurred at the site of simple closure of the fistula, with bronchopneumonia supervening; in the third, peritonitis followed a wound infection at the site of the initial transverse colostomy. This was after the fistula had been resected at the second stage. In the fourth, death was from staphylococcal bronchopneumonia. This patient had, in addition, a carcinoma of the large bowel. Three of the deaths occurred in patients who were in poor shape; four, in those who were emaciated. It is not possible, however, to say that those who survived were all in better preoperative shape. It is possible to say that when the presence of the fistula was immediately noted and the patient operated on before his condition deteriorated, the course was uneventful.

Correlation of Symptomatology with Pathology

It is apparent that food can pass out of the stomach into the small bowel by either the pylorus, if it is still present, or the stoma; or that it can pass to the colon directly by a gastrocolic fistula. Alternatively, it may pass to the colon and jejunum simultaneously by a gastrojejunocolic fistula, or it may pass to the jejunum and then to the colon by jejunocolic fistula. Similarly, colonic contents can pass to the stomach, to the stomach and small bowel simultaneously, or to the small bowel. The route will be dependent on the site of the fistula. Certain additional factors might determine the direction of passage of food or colonic content. These are the size of the opening, the posture, the presence of folds of mucosa at the fistula, acting as valves, the normal peristaltic course, and the pressures within the lumen of the stomach, jejunum, and colon.

The size of the opening does not appear to influence the pattern of the symptoms. This has been the finding of others as well. In 12 specimens in which the size was recorded, it ranged from 0.5 to 4 cm., though the usual size was about 1-2 cm. (eight cases). However, the four patients with the largest fistulae all died, and their condition appeared to be worse.

It has been suggested that posture accounts for the occurrence of nocturnal diarrhea. But nocturnal diarrhea was an inconstant feature, and it is difficult to find any correlation.

A valvular action has been postulated to explain the inability of the barium swallow to reveal the lesion, whereas barium enema will do so. Such an action is unlikely. Radiologists have never been able to show this valvular action, and four fresh specimens examined have shown no valves. In fact, the surrounding scar tissue tends to hold open the openings. It is a more likely explanation that the barium enema is run in under a head of pressure which is enhanced by a competent ileocolic valve and is higher than any normal intestinal pressure. It therefore escapes by any opening, that is, the fistula. The barium swallow, however, is dependent on normal peristalsis to carry it onward, preferably by its usual channels. If there is no gastrocolic opening, barium is likely to be carried along the normal peristaltic pathway, and relatively little will pass into the colon through the jejunocolic open-

ing. If, however, there is a gastrocolic opening in addition to the gastrojejunostomy, barium is likely to leave by each of these abnormal openings equally. The presence or absence of the pylorus is not likely to make much difference. A fistula just at the stoma is likely to produce the picture of both gastrocolic and jejunocolic fistulae. Differential pressures probably play little part, for pressures within the peritoneal cavity are the same everywhere. When there are fistulous openings between parts of the bowel, the pressures on the two sides of the opening are not likely to vary greatly.

The fistula was demonstrated in 19 patients by barium enema. Sixteen patients had barium by mouth. In 12 patients the fistula was not demonstrated, whereas in 3 the barium passed into the colon freely. Two of these patients had frank gastrocolic fistulae. In the third the x-rays suggested a jejunocolic fistula. Unfortunately, the operative record and pathology specimen are not available, though the case was coded as one of a gastrocolic fistula. This patient has been included in the group in which the site of the fistula was indefinite. The third patient who had a definite gastrocolic fistula did not have a barium meal. Of the films available, a review of four suggests the presence of barium in a loop of large bowel before the cecum was outlined. Of these fistulae, three were jejunocolic and one gastrojejunocolic. This finding suggests that the manipulations of the radiologist may force a small amount of barium through the fistula into the colon, but it emphasizes again the difficulty of displaying a jejunocolic fistula by a barium meal.

Site of Fistula

If one returns, therefore, to the anatomical site of the fistula, a pattern does become apparent (Table 4). Three fistulae were gastrocolic. In 11 cases it was between the efferent limb of the jejunum and the colon. In six it was at the stoma, a gastrojejunocolic fistula. In three the description was indefinite, and the site could not be decided for certain.

TABLE 4.—*Site of Fistula*

Gastrocolic	3
Jejunocolic efferent limb	11
Gastrojejunocolic	6
Indefinite	3

In patients with gastrocolic fistula the nature of the diarrhea was different. It was not as severe, and food seemed to go right through, since the stools were noted to contain undigested food. Two of these patients also had marked nausea, with fecal eructations and vomiting, that is, passage of colon content into stomach. Why the colon content does not then set up an enteritis is hard to say. It may be that the spill into the stomach is intermittent and the continual vomiting empties it out as fast as it appears. Acidity may play a part in sterilization, too, for of eight patients in whom acid levels were determined all had readings higher than normal. Only one of the gastrocolic patients had an acid level determined. The reading was 40 units of HCl. Barium by mouth will reveal the gastrocolic fistulae. One of the patients with gastrocolic fistula had a transverse colostomy. Stomach content continued to appear from the distal opening of the colostomy, producing excoriation of the skin. It did, however, relieve the nausea and vomiting, but his general condition continued poor.

If the cases of frank jejunocolic fistulae from ulceration are examined, the pattern is different. These had marked diarrhea, suggesting enteritis; fecal vomiting was unusual, though eructation of foul gases might be present; a barium meal showed the fistula with difficulty, if at all, and the barium enema, with ease. Here food passes through the stoma and continues down the intestinal tract. Colonic content passes into the jejunum and sets up an enteritis. Little passes by reverse peristalsis to the stoma, but foul gases may be belched up.

As might be expected, patients in whom the fistula was at the stoma share the patterns of both gastrocolic and jejunocolic fistulae.

Two patients whose fistulae were unequivocally jejunocolic had relief from proximal colostomy, in one case dramatic, with immediate cessation of nausea, vomiting, and diarrhea. Of the other two patients who had proximal colostomy without relief, one had a gastrojejunocolic fistula, with the fistula at the stoma, but mainly involving the stomach; the other had a frank gastrocolic fistula. The fifth patient with proximal colostomy had a jejunocolic fistula; but even when the fistula was closed, diarrhea continued up to her discharge from hospital.

Fistulae Occurring from Carcinoma

If the five cases of frank gastrocolic fistula from carcinoma are now examined, they show a pattern of foul eructations and vomiting similar to the gastrocolic cases from peptic ulceration. Diarrhea was present in only one case, and consisted of undigested food just eaten. In all cases barium swallow, as well as barium enema, demonstrated the fistula. It might be objected that these cases bear no relationship to those resulting from peptic ulceration; but, quite fortuitously, one of the carcinoma patients had had a gastrojejunostomy performed 10 months earlier and thus the case is quite comparable. He even had a proximal colostomy, with relief of the nausea and vomiting, but continued to have profuse, watery colostomy movements and watery rectal movements. The patient with the jejunocolic fistula from carcinoma had a clinical picture identical with that of the jejunocolic fistulae in peptic ulceration. Diarrhea was marked; vomiting and eructations were absent. Barium enema demonstrated the fistula with ease; barium meal showed a small amount of barium in the transverse colon with difficulty.

Comment

As has already been said, there is little difference of opinion concerning the principles of treatment of gastrojejunocolic fistula resulting from peptic ulceration. These are, first, to diagnose the case early, before malnutrition and dehydration make the patient a poor risk; second, to close the fistula, and, third, to prevent the recurrence of ulceration by an adequate ulcer operation. The major disagreement had been in the methods of making the patient fit for closure of his fistula.

The present series emphasizes again that the sudden onset of severe diarrhea in a patient who is known to have had a previous operation for peptic ulceration is the single most important symptom. The onset of diarrhea is usually preceded by other symptoms of recurrent ulcer, which may disappear with the onset of the fistula. This delay between the original operation and the onset of diarrhea helps to differentiate both postgastrectomy diarrhea and mistaken anastomosis. The occurrence of fecal eructations and foul vomiting is supporting evidence of a fistula, but may be absent. The simple therapy suitable for gastroenteritis will not relieve the patient, and it is imperative that a barium enema be carried out without delay. If delay in diagnosis occurs, rapid weight loss becomes obvious, together with other evidences of malnutrition.

A mistaken anastomosis, usually a gastroileostomy, but occasionally a gastrocolostomy, when associated with a patent pylorus, may have few or no symptoms; but when any are present, diarrhea is the most important. Such cases have been confused with fistula. When it is associated with partial gastrectomy, the clinical picture is very much that of fistula, with frequent diarrhea, foul eructation, and loss of weight, leading to emaciation. However, unless the ileocolic valve is incompetent, barium enema will not reveal a gastroileostomy; but a barium meal will, and should, supplement any case which remains in doubt. A gastrocolostomy will be revealed by either investigation.[4]

The diagnosis having been made, surgical correction is urgent. With the better understanding of preoperative preparation and the obvious disadvantages of multiple-staged operations, a single procedure has again become more popular; and there is little doubt that when the fistula is discovered

early, it can be repaired safely in one stage. The present cases support this contention. Time should be taken only for correction of fluid and electrolyte balance, and of anemia, and for preparation of the bowel. Little can be gained by any attempt at conservation management; and in the present series enemas, opium, and dietary and other means of controlling the diarrhea had no effect. The best results were obtained with such a single-stage procedure. Of nine patients, only one died, and he had a carcinoma of the ascending colon in addition.

It has also been brough out well in the literature and in this series that the single-stage procedure must incorporate measures designed to reduce the gastric acidity. At present this is probably best done by an adequate (four-fifths) partial gastrectomy, or, in those cases with a previous gastrectomy, revision of the gastrectomy and vagotomy. All four patients who failed to have this done developed recurrent ulceration, and three, recurrent fistulae.

The problem, however, remains as to what is the best procedure for those patients who are quite unfit for a single-stage operation.

For many years it was thought that, in the words of Sir David Wilkie,[5] "the regurgitation of faecal matter into the stomach destroys all appetite for food, leads to a characteristic anaemia, and the entry of partially digested food into the colon causes persistent diarrhoea and loss of weight." In 1939 Pfeiffer[6] postulated that, in fact, it was irritation of the small bowel by colonic contents, a true enteritis, which produced the diarrhea, and this led him to suggest a proximal colostomy as the logical first stage. This procedure also helped to alleviate the perils of peritonitis from primary colon anastomosis in those days. But, in fact, his work had been anticipated by those careful observers Bolton and Trotter,[7] who, as early as 1920, pointed this out and recommended a preliminary cecostomy. Nevertheless, Pfeiffer deserves the credit for his advocacy of the proximal colostomy. But it is significant that, in his series, 4 cases out of the 15 appeared to have no marked improvement from the colostomy as far as diarrhea was concerned. Of these four patients, two had frank gastrocolic fistulae.

It is, therefore, in those patients who are not fit for a one-stage procedure that the preoperative differential diagnosis of gastrocolic and jejunocolic fistula becomes important. The gastrocolic fistulae failed to benefit from proximal colostomy; the jejunocolic fistulae did. The differing clinical picture will arouse suspicion, and a barium meal should supplement the barium enema. If the fistula is shown with ease by the barium meal, the fistula is likely gastrocolic, or gastrojejunocolic, with the predominant portion of the fistula on the gastric side of the stoma.

Those patients who have frank jejunocolic fistulae should have a proximal colostomy, placed in either the ascending or the right transverse colon. Those patients who have a gastrocolic fistula should not. Luckily, such patients are few and seem to be in better shape than those with a jejunocolic fistula. But if it is not prudent to do a one-stage resection in these gastrocolic fistulae, some form of colonic exclusion would seem to be preferable to proximal colostomy. Wilkie[5] advocated the isolation of the portion of colon containing the fistula, with end-to-end anastomosis of the proximal and the distal colon. Of four patients noted in the literature to have been treated in this way, two had a marked relief of symptoms. Two, who were desperately ill, died.[1]

Lahey[8] suggested, to avoid the disadvantage of an external fecal fistula, the performance of an ileocolostomy, end-to-side, between terminal ileum and descending colon. The second stage included right hemicolectomy and resection of the fistula. On theoretical grounds, it is unlikely that this procedure would be of value in gastrocolic fistula. It would perhaps have been the preferable procedure for the patient who had a carcinoma of the ascending colon in association with his fistula.

It is in the treatment of gastrocolic fistula due to carcinoma that the question of proximal colostomy is likely to arise. Resection, if it is possible, provides the best symptomatic relief, and sometimes surprisingly long survival. Many have held that when the lesion is not resectable the life expectancy in these patients is so short that either nothing should be done or a proximal colostomy should be carried out. Of the patients in this series whose lesions were not resectable, all died within six months. Two had a transverse colostomy, without relief of their symptoms, and with the added distress of the colostomy. The sixth patient, however, had a "sidetracking operation." The loop of transverse colon containing the fistula was isolated, the proximal end closed, and the distal end anastomosed with the proximal jejunum. The colon continuity was then restored by end-to-end anastomosis. He survived, with marked relief, for five months and then died suddenly of a perforation of the colon due to the carcinoma. A review of the operative findings in the other cases suggests that this would have been feasible in four patients at least, and would have been attended with better results.

Fortunately, the incidence of gastrojejunocolic fistula is decreasing, as adequate gastric resections replace gastrojejunostomy in the treatment of peptic ulcer. Nevertheless, if only 2 patients in every 100 subjected to partial gastrectomy develop recurrent ulcer, and if the incidence of fistula complicating recurrent ulcer is taken at the rather low rate of 8.7%,[9] then 2 patients in every 1,000 undergoing gastrectomy are likely to develop a fistula. As partial gastrectomy has displaced gastrojejunostomy only in the last 20 years, cases are still likely to occur as a complication of the latter operation.

Summary

Twenty-four gastrojejunocolic fistulae occurring in 21 patients following surgery for peptic ulceration are reviewed. Six fistulae resulting from carcinoma have been considered separately.

The most important symptom is the onset of diarrhea in patients who have had previous surgery for peptic ulcer. Such patients should have a barium-enema examination early.

Barium enema confirmed the diagnosis in all cases in which it was employed.

The best results of treatment were obtained by early single-stage operation to resect the fistula, and to reduce the possibility of recurrent ulcer by adequate partial gastrectomy, with vagotomy if necessary, in those patients who were fit for such major procedure.

Proximal colostomy appears to benefit only those whose fistula is jejunocolic. Patients with a gastrocolic fistula are not improved. Gastrocolic fistulae are best revealed by barium meal.

Patients with gastrocolic fistula due to carcinoma are not relieved by proximal colostomy. If the lesion is not resectable, they are best treated by a "sidetracking" operation to exclude the portion of colon involved.

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Effect of Antibacterial Agents on Clean Wounds

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Substances for local application to wounds continue to be offered and frequently recommended as adjuncts to epithelization, despite the known facts that chemicals applied to wounds generally retard their healing. Lister first recognized that his antiseptic agents often delayed rather than supported wound healing, and thus began the emphasis upon asepsis, rather than antisepsis. The sulfonamide drugs were widely used in wounds until clinical and experimental studies revealed them to be deleterious. Even with this, as each new antimicrobial agent is discovered, an ointment is invariably promoted for application to wound surfaces. These agents must be appraised, as they appear, in order that no harm should be done through their use.

The study of the healing wound and inflammation has attracted many investigators, in an effort to understand better the physiologic processes involved. From these studies have come elaborate methods for following the wounds and discerning the processes. For the evaluation of the effects of the substances concerned in this study, a simple method was sought, and none better could be found than the method of Alexis Carrel, in which the progress of the wound is followed by mensuration of the surface area upon sterile cellophane. In his experiments, from 1900 to 1920, he demonstrated that wounds heal by contracture and epithelization and that the rate is proportional to the area of the wound. He also demonstrated that cicatrization of a wound is greater at the beginning than at the end of the period of repair, depending upon the area, rather than the age, of the wound.

In this experimental study, young male guinea pigs, obtained from a single source, were anesthetized with ether, strapped to a flat surface, and the hair shaved from the abdomen. The shaved area was prepared with hexylchloro-*m*-cresol. Elliptical portions of skin were excised on both sides of the midline, one to serve as the experimental wound and the other as the control wound. The areas excised were then traced upon sterile cellophane placed over the defects, which were then labeled and later traced upon plain paper, providing a serial representation of the rate of the healing of the wounds. A rayon dressing was applied to the control wound, and the test substance was applied to the experimental side. These were covered with gauze, and the entire dressing was then made secure with 3-in. adhesive tape and appropriately labeled. On alternate days, the animals were anesthetized and the dressings removed. Mensuration of the wound area and reapplication of the dressings were carried out as on the first day, until healing was complete. Twelve animals were utilized for each test substance. If during the course of the experiment more than two animals died, the experiment was repeated, so that each antibacterial agent was tested on at least 10 guinea pigs.

Seven antibacterial ointments were tested: tetracycline (Achromycin), chlortetracycline (Aureomycin), bacitracin, chloramphenicol (Chloromycetin), neomycin, polymyxin B, and oxytetracycline (Terramycin). Each of the ointments was obtained from the pharmacy as a standard preparation offered by the manufacturer, with the exception of chloramphenicol, which was obtainable only in the ophthalmic preparation; thus a 3% ointment in a standard base was made up in our pharmacy and corresponded in strength to the other ointments.

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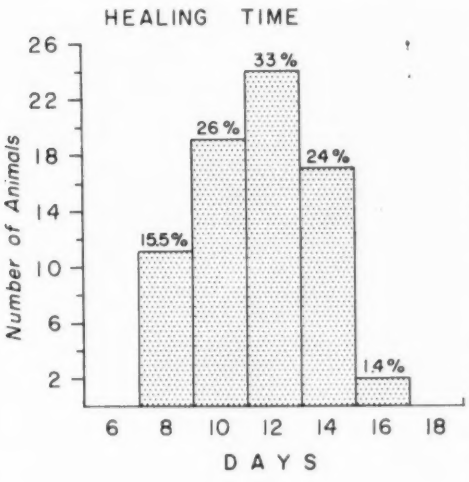

Figure 1

The control wounds responded as did those of Carrel, with contraction and epithelization. The rate was usually faster during the first three to four days than toward the end of the healing process. Of the 73 control wounds involved in the experiment, the distribution of the time of healing is demonstrated in Figure 1, in which it is seen that the majority of the

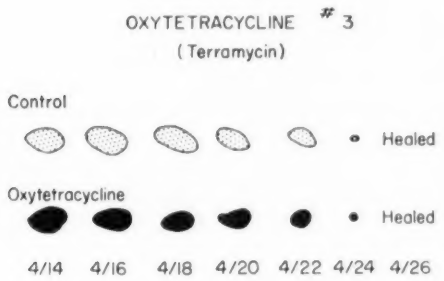

Figure 2

control wounds were healed between the 12th and the 14th day, with 15.5% healing on Day 8, while healing of only two wounds, or 1.4%, extended until the 16th day. The two largest wounds healed in 14 days. Figure 2 is a tracing of the wound surface areas on alternate days, from time of infliction to healing, representative of the entire experiment. One notes the gradual reduction in surface area, until healing is complete on the 12th day.

TABLE 1.—*Summary of Antibacterial Agents Used in Wound Healing*

Agent	Hastened	No Effect	Delayed	Conclusion
Tetracycline	0	10	2	No effect
Bacitracin	1	8	2	No effect
Chloramphenicol	0	8	2	No effect
Neomycin	0	8	2	No effect
Polymyxin B	0	10	0	No effect
Oxytetracycline	0	9	1	No effect

As for the effects of the antibiotics tested, generally there was no effect noted. Table 1 is a summary of the agents used. Tetracycline had no effect upon 10 animals, while it delayed healing in 2, with an over-all "no effect" upon wound healing. Bacitracin then hastened healing in one animal, had no effect upon healing in eight, and delayed healing in one. Chloramphenicol had no effect upon 8 animals and delayed healing in 2; neomycin, no effect upon 9 and delayed healing in 2; polymyxin B sulfate, no effect upon 10, and oxytetracycline, no effect upon 9 and delayed healing in 1. From this it is seen that the antimicrobial ointments listed, in general, did not appreciably delay or hasten the rate of wound healing. However, chlortetracycline presented a different picture, for it delayed wound healing (Table 2). It delayed healing in nine animals, from two to six days, while in only one animal was it observed to have no effect. This experiment has been repeated, and the results of delayed wound healing have been corroborated. A comparison of the bases utilized in the ointments was made, and the base of the chlortetracycline ointment was found to be identical with the base of four of the other ointments. Figure 3 is a

TABLE 2.—*Effect of Chlortetracycline (Aureomycin) on Wound Healing*

Agent	Hastened	No Effect	Delayed	Conclusion
Chlortetracycline	0	1	9	Delayed

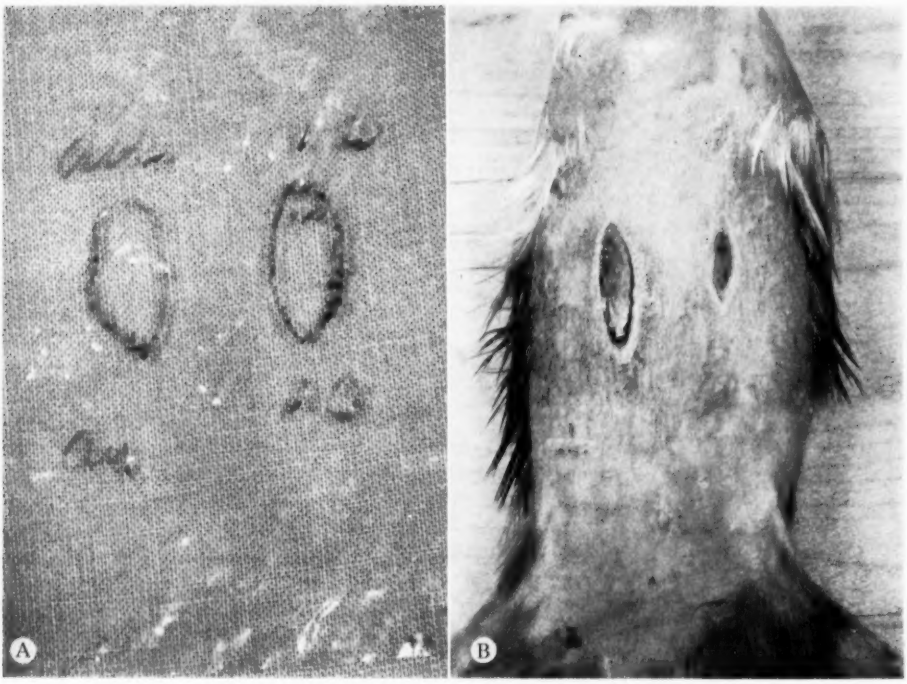

Fig. 3.—Chlortetracycline (Aureomycin)-treated experimental animal. *A* shows the size of the wounds when created, as traced upon the cellophane. *B* shows the appearance of the wounds 10 days later, demonstrating the marked difference between the chlortetracycline-treated wound (larger) and the control wound (smaller).

photographic illustration of the delay in wound healing encountered with the use of chlortetracycline ointment.

Summary

It was found that the antibacterial agents tetracycline (Achromycin), chlortetracycline (Aureomycin), bacitracin, chloramphenicol (Chloromycetin), neomycin, polymyxin B, and oxytetracycline (Terramycin) generally do not retard or accelerate the rate of wound healing, with the exception of chlortetracycline, which was found to retard routinely the time for healing from two to six days.

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Adenocarcinoma of the Jejunum in Nonspecific Granulomatous Enteritis

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Nonspecific granulomatous ileitis, as a distinct entity, was described for the first time by Crohn, Ginzburg, and Oppenheimer in 1932.[1] References to this disease are made in the literature as far back as 1769, by Morgagni,[2] and in 1913 by Dalziel,[3] and in 1923 by Moshcowitz and Wilensky.[4] The disease is not uncommon, with Marshak and Wolf [5] reviewing 750 cases from the Mount Sinai Hospital in New York in 1955 and Van Patter, Bargen, et al.[6] reporting on 600 cases from the Mayo Clinic in 1954. The incidence of malignancy in the small bowel in nonspecific granulomatous enteritis is extremely low. The first case reported was that of Ginzburg et al. in 1956,[7] with an adenocarcinoma seen in the jejunum and multiple metastases to the liver. The inflammatory disease in the small bowel appeared to have been present for 15 years, from the history, and, by actual roentgenographic demonstration, for 4 years before the appearance of an adenocarcinoma in the jejunum.

The second case reported was that by Kornfeld, Ginzburg, and Adlersberg,[8] in 1957, again with adenocarcinoma seen in the jejunum in a case of nonspecific granulomatous jejunitis. This second case was observed in a 36-year-old white woman, whose initial symptoms and physical findings were noted eight years prior to admission, when she was 28 years of age. At the age of 34, in 1953, a roentgen diagnosis of segmental enterocolitis was made, with a number of involved loops present in the proximal jejunum and with the typical findings of regional ileitis in the terminal ileum. Two years later, as seen by roentgen examination, a zone of marked narrowing of the jejunum, just distal to the ligament of Treitz, was described, with marked dilatation of the duodenum proximal to the site of the narrowing. At surgery, the area of narrowing proved to be adenocarcinoma of the jejunum. A radical resection was not possible, and a retrocolic anastomosis was performed, bypassing the area of carcinomatous involvement. The patient died five months after operation, with widespread metastases.

The third case, reported by Bersack, Howe, and Rehak,[9] concerned a 26-year-old white man with clinical and roentgen evidence of granulomatous enteritis for at least 9, and possibly 11, years. This patient developed diffuse adenocarcinoma involving the duodenum, jejunum, ileum, and ascending colon, with extensive metastases. The authors stated that no typical histologic evidence of regional enteritis could be identified, although nonspecific inflammation was present throughout. Aberrant pyloric-glands were found in a section of the ileum. (Such aberrant glands were described by Liber [10] in 1951 in four out of five cases of regional

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enteritis.) Nothing else to indicate granulomatous enteritis was described by Bersack et al. in their case. The validity of this case as an example of adenocarcinoma occurring in enteritis is therefore open to question, although the roentgenograms reproduced strongly suggest a preexistent inflammatory process.

Adenocarcinoma of the jejunum *de novo* is a rare disease.[11-13] The occurrence of adenocarcinoma of the jejunum in a case of long-standing nonspecific enteritis suggests the possibility of a relationship between the two entities, possibly based on the same kinds of chronic irritative phenomena that are seen in the development of carcinoma in chronic ulcerative colitis. The latter combination is well known, with different series reporting an incidence of malignant degeneration varying from 5% to 20%.

Van Patter et al. report that colonic involvement in regional enteritis, which occurred in their series in 37% of all patients, was associated with malignant change in the colon in only 1 case out of 600. Marshak and Wolf state that in regional enteritis "an uncommon but striking finding is the presence of large, inflammatory polyps. . . . Carcinomatous transformation of these polyps has not been observed."

The following case represents the third authenticated reported instance of adenocarcinoma occurring in the jejunum in chronic nonspecific granulomatous enteritis and the first reported instance of adenocarcinoma arising in a "bypassed" small-bowel loop. This case has been under constant observation by one of us (B. W.) for 21 years.

Report of a Case

Clinical Summary.—A 44-year-old white woman entered Montefiore Hospital for the fifth time on July 30, 1956, because of ascites, of four weeks' duration. The history dated back to 1929, when, at the age of 16, she suffered a severe attack of purulent tonsillitis, after which she developed alternating periods of diarrhea, constipation, and abdominal distention, which lasted two years. In 1931, she was subjected to an exploratory laparotomy in another hospital, with findings reported "typical of tuberculosis" on biopsy, although no actual tubercles were found in the jejunum. She was transferred to a second hospital, where a diagnosis of tuberculosis could not be substantiated, and she was discharged after three months. In 1936, she was admitted to a third hospital, where an upper gastrointestinal series was suggestive of multiple small-bowel strictures. Sidetracking anastomoses were advised here as the procedures of choice; this advice was refused. She was admitted to Montefiore Hospital for the first of her five admissions, in 1937, and conservative treatment was instituted. She was dicharged and readmitted for a laparotomy. On this second admission, at the time of surgery, in 1938, the small intestine showed areas of constriction and dilatation at the junction of the jejunum and the ileum, and an indurated loop of jejunum was seen. A jejunojejunostomy with a blind loop remaining was performed at this time. She did well postoperatively for about four years, with three to four loose stools daily. She then suffered a recurrence of symptoms, with watery diarrhea and a 35-lb. weight loss. She was readmitted to Montefiore Hospital for the third time, in 1942, treated conservatively, with improvement, and was discharged to the outpatient department. She was followed by periodic roentgen studies of the small intestine, which showed an

Fig. 1.—A roentgenogram of the abdomen exposed two hours after the oral ingestion of barium in May, 1943, shows multiple zones of narrowing and segmental dilatation of the jejunum and ileum, indicating chronic granulomatous nonspecific enteritis.

increasing degree of stricture and dilatation of the jejunum, with delayed emptying (Fig. 1).

In 1948, small-bowel studies again showed "chronic regional enteritis with stricture, dilatation, subacute intestinal obstruction, multiple string signs and skip areas." The colon was reported as showing only spasticity, with no organic disease. During this period, between 1937 and 1942, the patient had married and had given birth to two normal children. Following the third admission and discharge to the outpatient department, she did well, until 1956, when, again, there was a recurrence of symptoms, with a 19-lb. weight loss. Since 1951, the patient had been maintained intermittently on steroids. Small-bowel roentgen examinations were obtained through the years (Fig. 2). Because it was felt that she had an obstruction, another jejunojejunostomy was performed on the fourth Montefiore Hospital admission, in 1956. At operation at this time there "appeared to be a closed loop, because of a series of constricting adhesions." The mesentery was thickened, with the sensation of a mass posteriorly, but, because of the patient's poor condition, this was not investigated more closely. Some omentum was removed at this time, and the pathologic report was "metastatic adenocarcinoma in the omentum." Postoperatively, there was a remission of the abdominal symptoms, but the patient developed bilateral thrombophlebitis. At her own request in May, 1956, she was discharged to her home, where she was treated conservatively. One month prior to the present (fifth) admission, and three weeks after the surgical procedure on the fourth admission, the patient noted the onset of increasing distention and anorexia.

On this fifth, and last, admission, her temperature was 99.6 F, pulse 108, blood pressure 98/64, and respirations 24. She was cachectic and in acute distress from the abdominal distention. The pertinent physical findings included a soft, dry skin; a pale, moist oral mucosa with a smooth, beefy tongue; a distended abdomen with marked superficial venous distention; abdominal scars from previous surgery, and an enlarged liver (5 fingerbreadths below the right costal margin). There were tumor implants in some of the abdominal scars. The stool was soft, fatty, silvery and foul-smelling. The pertinent laboratory data showed a secondary anemia (hematocrit, 27%) with a white cell count of 10,000 per cubic millimeter and a shift to the left. A roentgenogram of the chest showed focal atelectasis in the left base. A barium enema showed narrowing of the rectosigmoid junction, probably due to extrinsic pressure, with a normal colonic mucosa. On the roentgenograms of the abdomen obtained during the barium enema, several markedly dilated loops of jejunum outlined with air were noted in the left upper quadrant, with segmental areas of narrowing (Fig. 3). The fluid

Fig. 2.—A film of the abdomen in April, 1956, during a small-bowel series, shows a zone of narrowing in the midjejunum, with marked proximal dilatation. The mucosa at the site of narrowing appears effaced.

Fig. 3.—A film of the abdomen during a barium enema in August, 1956, shows markedly dilated loops of midjejunum distended with air, with intervening zones of narrowing.

Fig. 4.—Gross pathologic specimen, showing "bypassed" jejunal loop, studded with tumor nodules on the mucosal surface.

obtained by abdominal paracentesis showed fragments of adenocarcinoma.

The patient ran a low-grade fever throughout her course. Repeated abdominal paracenteses were productive of considerable fluid. She was treated symptomatically, and on the 11th hospital day she suddenly died, after complaining of low-chest pain radiating to the left shoulder and back.

Autopsy Report

The pertinent findings on autopsy were as follows: The patient showed no evidence of myocardial infarction or pulmonary embolus, both of which were suspected terminally. The important findings were those referable to the abdomen. From the ligament of Treitz, the jejunum for approximately 20 in. appears to be extremely dilated in its diameter. The walls are thickened; the serosal surfaces are studded with white tumor nodules, and the mucosal pattern appears to be hypertrophic, with long, edematous, luxuriant folds, which appear to be more prominent than is usually seen. At the end of this dilated portion of the jejunum an old loop anastomosis is observed. In this bypassed anastomotic loop, a greatly thickened jejunum is present, with fat seen to grow over the surface of the entire mesenteric border. Tumor nodules are scattered throughout the serosal surface. On opening this section of bowel, three strictures are observed within the bypassed loop. The mucosa is rather granular and friable in appearance, containing many nodules along its surface (Fig. 4). A second loop anastomosis is observed, approximately 10 cm. below the first anastomosis. This is much fresher in origin and is seen to bypass the first anastomosis. Extending into the

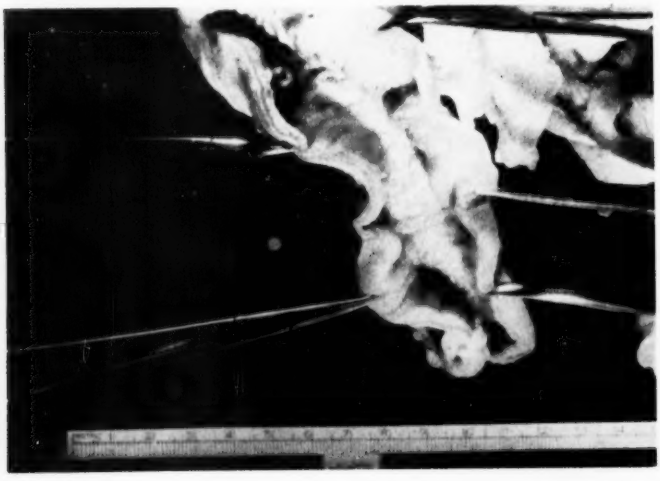

Fig. 5.—Gross appearance of the terminal ileum, showing profound thickening, indicating granulomatous ileitis.

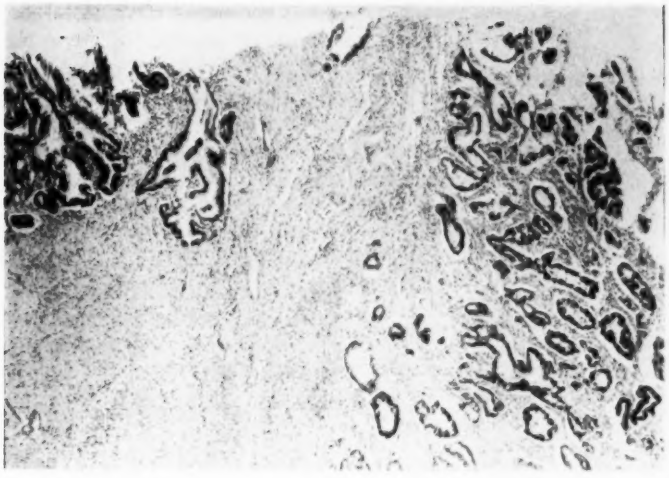

Fig. 6.—Low-power magnification, showing adenocarcinoma cells arising in the jejunum. Reduced to 62% of mag. ×80.

ileum, it is noted that there are multiple strictures involving the entire small intestine. Throughout its length, the serosal surface is studded with tumor nodules; the walls are greatly thickened, and mesenteric fat is observed to extend toward the antimesenteric border. It may also be noted that the entire length of the small intestine appears to be reduced. The terminal ileum is greatly narrowed by this thickened process (Fig. 5); the large intestine is patent throughout; its serosal surface is also studded with tumor implants. The colonic mucosa is normal.

The microscopic sections showed a moderate chronic inflammatory response present within the mucosa in specimens of the jejunum removed from the bypassed loops of bowel. The submucosa of the jejunum is greatly thickened and consists of dense bands of collagenous and fibrous tissue, of moderate cellularity. Several segments of jejunum removed from a bypassed bowel loop (the original bypass) reveal an adenocarcinoma arising from the mucosa and extending through the submucosa and muscularis. These sites appear to indicate multifocal origin for the tumor. The tumor consists of medium-to-large irregular and straight acini, occasionally filled with proteinaceous material and lined by several layers of medium columnar epithelial cells with scant, deeply eosinophilic, homogeneous cytoplasm and enlarged, irregular, hyperchromatic nuclei without nucleoli or mitotic figures (Figs. 6 and 7). The tumor rarely shows necrosis. In the ileum there is moderate mucosal atrophy with uniform chronic inflammatory infiltration. The submucosa appears wider than is usually observed and is frequently replaced by thick fibrous connective tissue. Other areas reveal

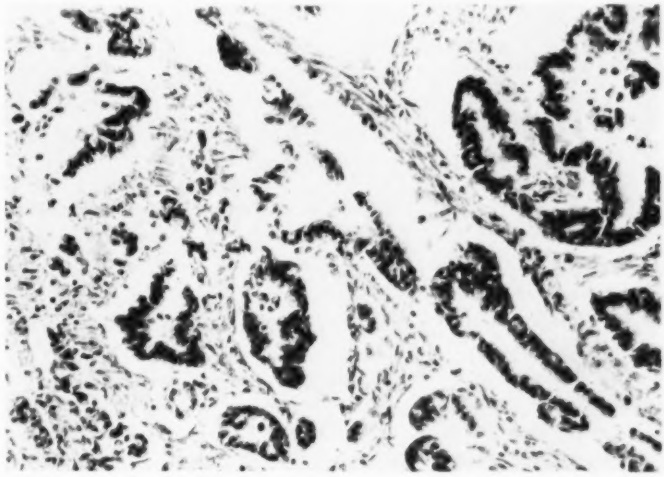

Fig. 7.—High-power magnification of adenocarcinoma cells in bypassed loop of jejunum. Reduced to 62% of mag. ×250.

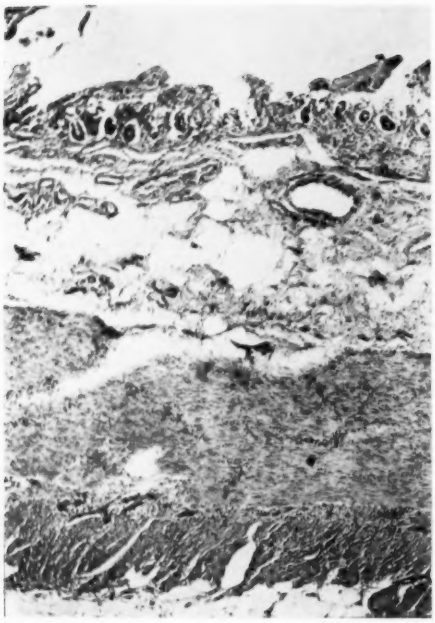

Fig. 8.—Microscopic appearance of markedly thickened wall of the ileum with replacement by fibrous connective tissue, indicating chronic granulomatous enteritis. Reduced to 56% of mag. ×80.

an increase in submucosal fat with marked dilatation in the lymphatic vessels. Focal accumulations of chronic inflammatory cells are present.

The final pathologic summary included regional enteritis involving the jejunum and ileum; scars of jejunojejunostomy, performed to bypass affected loops of bowel; adenocarcinoma of the jejunum arising in bypassed jejunal loops; metastases to regional lymph nodes, visceral and parietal peritoneum, liver, lungs, uterus, and ovaries; thrombosis of the common iliac vein and inferior vena cava; ascites; fatty liver; chronic ulcerative esophagitis, and focal pneumonia.

Comment

In the two previously reported authenticated cases of adenocarcinoma arising in the jejunum in instances of long-standing, chronic granulomatous enteritis and in our reported case, the disease had been present for a number of years before the advent of the adenocarcinoma. There was no preoperative roentgen or clinical diagnosis of adenocarcinoma made in these three cases. The roentgen findings ordinarily associated with neoplasm, consisting of mucosal destruction, ulceration, and rigidity, were not detected in advance. In the presence of long-standing inflammatory disease, such changes may be very difficult to delineate and appreciate, since they may be present during the course of the inflammatory process. Zones of narrowing with proximal obstruction are frequently found in the inflammatory process, without carcinoma being present. Loss of weight and other clinical stigmata of a neoplastic process may also be seen in chronic granulomatous enteritis. The roentgen and clinical diagnosis of a complicating adenocarcinoma in this disease entity is therefore extremely difficult.

As indicated above, the occurrence of carcinoma in a bypassed segment of chronically inflamed bowel is reported for the first time. With modern medical therapy, including steroids, antibiotics, transfusions, etc., increasing numbers of patients with chronic granulomatous enteritis with increasing longevity are to be expected. The problem of doing a bypass operation and leaving intact in the abdomen a segment of chronic inflammatory disease, as against the alternative of resecting the entire diseased bowel area, must now be considered.

We hope that, with this presentation, the gastroenterologist, radiologist, and surgeon will be alerted to the possibility of the occurrence of adenocarcinoma in a segment of granulomatous enteritis and will consider this potential complication in evaluating therapy.

Summary and Conclusions

A case of adenocarcinoma arising in a bypassed loop of jejunum in long-standing, chronic granulomatous enteritis, observed personally by one of us (B. W.) for 21 years, is presented. The literature concerning this complication is reviewed. The possible relationship of adenocarcinoma to long-standing granulomatous enteritis, particularly in a bypassed loop, is considered.

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The Wire Suture of Blood Vessels

An Experimental Study

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Any one of such complications of blood-vessel suture as thrombosis, stricture, aneurysm formation, or dehiscence may lead to a fatal result. The threat of these complications is sufficient to warrant continuous search for new methods and improved techniques which will serve to avoid or to minimize them. In experiments described below, the use of stainless steel wire as a suture material for blood vessels has shown distinct promise in this regard.

The materials ordinarily used for blood vessel suture have been (1) very fine surgical gut, (2) fine silk, and (3) fine cotton. The use of surgical gut having now been generally abandoned because of the intense reaction along the suture line, the use of fine nonabsorbable suture material has become an established principle in vascular surgery. Silk has been used most widely. Cotton has also been employed satisfactorily. Stainless steel wire, however, appears to possess certain advantages: its inert character, the minimal foreign-body reaction caused by its presence in tissues, and the ease with which it is handled. An experimental investigation of the use of wire in operations upon blood vessels has been made and is reported.

Method of Study

Twenty mongrel dogs of approximately 40-50 lb. weight were used. Suture of the divided common carotid artery was employed as a method for comparing suture materials. Intravenous pentobarbital (Nembutal) sodium was used for anesthesia. With strict attention to asepsis and with great gentleness in all manipulations, the common carotid artery was exposed in the neck and cleaned of all surrounding tissue, including the adventitia. Two arterial clamps were then placed across the artery at an interval of 6 cm., and the artery was divided midway between the clamps. The ends of the vessel were flushed with isotonic saline to remove all clots. The continuity of the artery was then reestablished by end-to-end suture, using interrupted everting horizontal mattress sutures in all instances. These sutures were placed approximately 2 mm. apart, 16 to 20 interrupted sutures being required to accomplish the anastomosis. Fine (000000) arterial silk sutures was used in the anastomoses in 10 animals, and No. 40 stainless steel wire (monofilament) was used in the other 10. At intervals thereafter, ranging from one week to one year, the suture lines were examined carefully for dehiscence, thrombosis, aneurysm formation, and stricture formation.

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From the Department of Surgery, University of Texas Medical Branch.

Results and Comment

Neither with 000000 arterial silk nor with No. 40 stainless steel wire was there dehiscence of all or a part of the anastomotic suture line. Similarly, with neither technique did hemorrhage occur. Thrombosis was not a prominent feature whether silk or wire was used. In the series in which the sutures were of wire there was no evidence whatever of thrombosis at the suture line, and the line was smoothly covered with intima. In the series in which silk was employed thrombosis at the suture line was minimal and occurred only infrequently; the silk-suture lines, however, were not as smoothly covered with intima as was the case with wire.

Reaction surrounding the vessel at the suture line was more marked when silk was used, as evidenced by the difficulty in freeing the vessel from surrounding structures at the time it was removed for examination. Microscopic study of sections made at the

Photograph showing narrowing of silk-suture line (bottom) and smooth, regular, nonconstricted wire-suture line (top).

suture lines showed definitely less foreign-body reaction at the wire-suture lines than at the silk-suture lines.

Aneurysm formation occurred in 10% of the animals in each series.

Narrowing at the suture line was not found when wire sutures had been used. When silk sutures had been employed, there was a variable, but slight, narrowing; in no instance was there any marked stricture of the lumen (Figure). The difference is reaction of the tissues to the two suture materials probably accounts for this slight difference in the occurrence of constriction at the site of anastomosis.

The remarkable ease with which fine-wire suture is handled in blood-vessel repair deserves mention. Because of the smoothness of monofilament fine wire, the suture was found to pass through the vessel wall without detectable resistance. There was no dragging or snarling of the suture in stray bits of adventitia; therefore, the holes in the vessel wall were small and smooth, and there was no oozing of blood. Consequently, lubricating the wire-suture material with liquid petrolatum U. S. P. was found to be unnecessary. The facts that no bits of adventitia were dragged into the suture line by the smooth wire and that the suture holes in the vessel wall were very regular may be among the reasons for the absence of any thrombosis at the line of anastomosis.

Bahnson, Spencer, and Bennett [1] have recently reported a series of five cases of staphylococcal stitch abscess of the myocardium or great vessels following surgical procedures. These stitch abscesses occurred around silk sutures, which acted as foreign bodies. It is possible that wire-suture material could eliminate this complication. Studies along this line are to be carried out in the near future.

It is agreed that the most important principles in the technique of vascular surgery are gentleness in handling the vessels and delicacy in surgical manipulation. The type of suture material employed in any one instance can be only secondary in importance. However, this experience with the wire suture of blood vessels has been most encouraging, and the advantages of wire suture in general are thought to be applicable in vascular surgery.

University of Texas Medical Branch

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Prednisolone (Meticortelone) in Treatment of Epicondylitis

Radiohumeral Bursitis and Radiohumeral Synovitis

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Epicondylitis of the humerus is commonplace, and yet often misdiagnosed and subsequently mistreated. On this premise, the following study of 391 patients with this condition has been undertaken. Actually, the cause of this pathology is unknown, although direct trauma, repeated shearing movements of the upper extremity, etc., are often described as etiological factors. By way of contrast, the lateral epicondyle is involved in the vast majority of cases, and the medial epicondyle is only occasionally involved as the site of this malady.

Tennis elbow, which is a rather hackneyed phrase, actually can be one of two types of pathology. The commoner type involves the common extensor tendon of the forearm at its origin on the lateral epicondyle of the humerus. This entity may be referred to by various titles, such as lateral epicondylitis, epicondylitis externa, and epicondylalgia (external). The more infrequent lesion involves structures with a synovial lining. There are two main types of this infrequent condition.

1. A bursa, which is inconstantly present between the common extensor tendon and the radial head, referred to as *radiohumeral bursitis*. Up to 1936 only 12 cases had been reported in the literature.

2. A synovial fringe, which extends from the synovial lining of the elbow articulation internally to be placed between the capitulum of the humerus and the head of the radius. This type has been named by Moore [13,14] *radiohumeral synovitis*. His report of 200 cases emphasizes the prevalence of this condition. Apparently, the synovial fringe, which is constantly present between the humerus and the radius, causes pain *only* by unusual positions of the arm. The unusual position most commonly implicated is supination of the forearm with a concomitant extension of the elbow: for example, the follow-through of a back-hand tennis stroke. In this manner, the radius and humerus come in contact with each other, thereby compressing the synovial fringe between them. It is the chronicity of the condition that makes it important for it to be correctly diagnosed and treated.

Physical therapy, including whirlpool, diathermy, microthermy, massage, ultrasonic therapy, etc., and even long periods of immobility using plaster casts, is of no avail.

Genesis

Direct violence to the lateral epicondyle is not thought to be a major factor in the etiology of tennis elbow, although Meherin and Cooper [10] found that this was a "mechanism of injury in a ratio of better than 2:1" in their cases. Certainly, in a radiohumeral bursitis and synovitis, the main contributing factor seems to be that of repeated strain and/or irritation due to some muscular activity and unusual position of the upper extremity.

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Meticortelone was provided for this study by courtesy of The Schering Corporation, Bloomfield, N. J. Nesacaine was provided for this study by the Maltbie Laboratories Division, Wallace & Tiernan, Inc., Belleville, N. J.

The age incidence is between 20 and 60 in most cases, with the majority of patients in the fourth decade of life. The sex incidence seems to be predominantly masculine.[10,13,14]

Discomfort is more commonly found in the major arm and is therefore generally in the right arm. It does appear to be commoner in people whose occupations involve repetitive flexion and supination.[19]

Clinical Signs and Symptoms

The most constant finding in tennis elbow is a small localized tender spot either adjacent to the lateral epicondyle, as is present in lateral epicondylitis, or centered near the groove between the humerus and the radius, as in the rarer cases of radiohumeral bursitis and synovitis. Pain may radiate up the arm or down into the forearm, but there always seems to be one local area near the actual site of the lesion which is especially tender upon digital pressure. These patients usually complain of well-localized pain.

Confirmatory tests include the following:

A. Lateral Epicondylitis

1. Increased pain produced over the site of the lesion when, with the elbow in extension, the wrist is dorsiflexed against some sort of applied resistance or the extensor muscles are passively stretched.

2. Inability to pick up an object when the forearm is pronated without experiencing pain over the lateral epicondyle.

B. Radiohumeral Synovitis

The act of supinating with the elbow extended and the fingers flexed will pinch an already thickened hyperemic synovial fringe and elicit pain in the groove between the humerus and the radius.

Pathology

The characteristic microscopic finding in lateral epicondylitis is one of patchy hyaline degeneration in the muscular and tendinous tissue which represents the common extensor tendon. According to Furlong,[5] the cells of the tendon stain poorly, and, in addition to hyaline areas, there are occasional small hemorrhages and patches of fibrosis. "The picture is one of local degeneration with gradual replacement by scar."

In pathological sections of the common extensor tendon, Meherin and Cooper[10] found "slight increase in the smaller vessels and an increase in cells." Many of their sections also showed some calcium deposits in amounts which were "too small, too few, and too scattered to be detected by x-ray examination."

The histologic picture in those cases involving the synovial fringe may be one of acute inflammatory reaction. In many cases the acute stage passes on to a chronic state. "The neighboring capsule and muscles become secondarily involved and, in rare cases, the periosteum." Complications which may follow are the formation of adhesions and patchy thickening of the synovial membrane.

The pathology of radiohumeral bursitis has not been adequately investigated. Presumably, the lesion is one of inflammatory response to unusual strain on the bursa which forms inconstantly between the common exterior tendon and the radiohumeral joint.

Treatment

The treatments devised for tennis elbow have been diverse, ranging from the manipulations of Cyriax[3] or Mills[12] to the injection of procaine into the site of the lesion. Most of the surgical techniques have been variations on the basic procedures established by Osgood[16] or Hohmann.[6]

Our main consideration in this study is with the value of prednisolone (Meticortelone) acetate in the treatment of tennis elbow. The rationale behind this treatment is the anti-inflammatory action of local injections of prednisolone in such diseases as rheumatoid arthritis.

Table 1 is a summary of the efficacy of local injections of prednisolone in the cases which have been reported in the literature. In the compilation of Table 1, there were many variations which were ignored in order that at least a preliminary picture of

TABLE 1.—*Results with Local Injections of Prednisolone*

Names of Investigators	No. of Cases Reported	No. of Cases with Apparent Lasting Improvement		No. of Cases with Little or No Lasting Improvement	
		After One Injection	After Two Injections	After One Injection	After Two Injections
Cyriax & Troisier [2]	12	10	12	2	0
Freeland & Gribble [6]	9	4		5	
Hollander [7]	25	22		3	
Murley [16]	19	14	16	5	3
Quin & Binks [17]	31	22	24	9	7
Stein, Stein, & Beller [21]	5	4	4	1	1
Young, Ward, & Henderson [23]	13	4	5	9	8
Totals and percentages	114	80/114 70.2%	61/80 76.3%	34/114 29.8%	19/80 23.8%

the effect of prednisolone in this condition might be presented. Owing to variation in the time interval that patients were followed after the injection, and depending upon the respective investigators, no time limit could be imposed on the data presented. Some investigators, such as Cyriax and Troisier,[2] believe that recurrence of tennis elbow does not occur. Consequently, with immediate relief of symptoms, they cease following the progress of the patients. Other workers, such as Young, Ward, and Henderson,[23] found recurrence of symptoms from one to five months after injection. Some patients, therefore, were followed for 10 days; others, for 5 months.

Other variables, which are at this time inherent in such a compilation, and which should be minimized as much as possible in future investigations are the following:

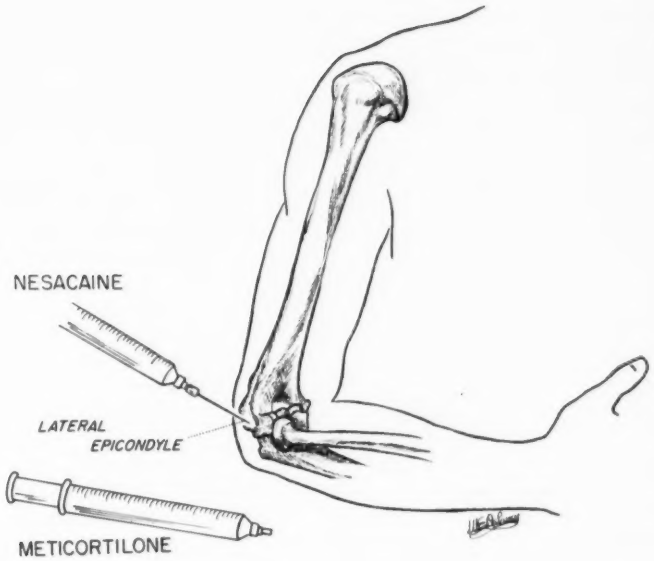
1. Some investigators injected procaine immediately prior to the injection of prednisolone; others did not.

2. Although the site of injection was always either at the site of tenderness or immediately adjacent to it, the type of tennis elbow being treated with prednisolone was not made clear in many cases reported. Prednisolone may not be effective to the same degree in all cases. For example, the cases in which prednisolone seemed efficacious may have included a great number of cases of radiohumeral synovitis and only a few of lateral epicondylitis. There is the possibility that cases of radiohumeral synovitis might have responded in which the injection was made intra-articularly, as it was in Hollander's subjects.[7] Nevertheless, it appears from present observations that prednisolone is effective in both types. All of the 12 cases of Cyriax and Troisier [2] were of the lateral epicondylar type. All of the 25 cases of Hollander [7] were of the radiohumeral synovitis type.

Cyriax and Troisier report an 83.3% cure rate with one injection and a 100% cure rate with two injections. Hollander reports an 88% cure rate with one injection.

The actual degree of improvement was taken into account by a few authors. Admittedly, such a concept as degree of improvement is difficult to express. Young, Ward, and Henderson [23] made an excellent attempt at classification of this sort. It was perhaps because of this rigorous classification that their results came out so adversely to the efficacy of prednisolone. The fact remains that some common definition of what constitutes "improvement" in these cases should be decided upon in order that a more meaningful picture of the usefulness of prednisolone can be gleaned. Some investigators gave one injection of prednisolone; others did not, and these varied as to length of time. Some authors, for example, Cyriax and Troisier,[2] advised their patients to avoid activity for at least a few days after injection of prednisolone. Others did not give this advice.

Since tennis elbow is believed by many to heal spontaneously, it may be that time and abstinence from the offending activity which causes the lesion initially, and not the prednisolone, may cause reduction of symptoms. Perhaps the two treatments together obtain a curative threshold which was not attainable by either one alone in terms of a short period of time.



Diagrammatic sketch demonstrating the site of injection.

Procedure

Technique.—The elbow is prepared aseptically in the usual surgical way, and then it is either fixed at right angles or fully extended. When effusion is present, the bulge of the synovium is noted on the exterior surface lateral to the olecranon process of the ulna. A size #20 needle is inserted just lateral to the olecranon and just distal to the lateral epicondyle of the humerus. A solution of chloroprocaine hydrochloride (Nesacaine) 1% is introduced into the periosteum prior to injection of prednisolone. This maneuver is preceded by a skin wheal, and then the deeper tissues are infiltrated with chloroprocaine 1%. The needle is left at the site of injection, and the contents of another syringe, of 1 to 1.5 cc. of prednisolone, are injected into the site.

Results

Because of misdiagnosis, and subsequent improper and inadequate therapy (for example, physical therapy), the following report of the treatment of 391 patients is offered; with the exception of 21 failures (one of whom underwent surgery) these patients were treated with local injections of prednisolone. All of the treatments were conducted in our offices. Of the 391 patients treated, 315 were men, and 76 were women, or a ratio of 4:1.

TABLE 2.—*Location of Pathology in (Epicondyle)**

	No. of Patients	Per Cent
Right lateral	346	88.5
Right medial	6	1.5
Left lateral	37	9.5
Left medial	2	0.5
Total	391	100

* Ten patients had bilateral involvement — not shown in the table.

Of the total of 391 patients treated, it is known that 330 were right-handed. The youngest patient was 21 years of age, and the oldest patient treated was 73. The majority were in the third, fourth, and fifth decades of life. Patients with bilateral involvement occurred in only 10 instances.

Usually, following the initial injection of chloroprocaine and prednisolone, the reaction was severe and very marked. On the evening following the injection there was required codeine grain 1 (60 mg.) to control evening pain. If at the end of one week the patient still had symptoms or objective findings, the injections were repeated. If no relief was obtained after the fourth injection, the treatment was abandoned and considered a failure. Initial

injection of chloroprocaine is important to relieve pain, and therefore it is given at the exact site of pathology.

In the one patient undergoing surgery, fasciotomy was resorted to, and its result was equivocal. It was thought that this patient had developed a strong functional overlay.

The results are tabulated as follows:

	One Injection	Two or more Injections
Excellent	215	90
Improved—fair results	40	15
Unimproved	25	6
Total	280	111

Average time for symptoms to disappear ..... 8-10 days
No. of patients receiving one injection .. 215
No. of patients receiving two injections . 111
Those complaining of residual symptoms on doing heavy lifting or strengthening exercises, etc., after one injection .. 65
Same after two or more injections ... 21

There were no untoward results or evidence of extreme allergy. A few patients receiving the injections did become lightheaded and dizzy, and it was recommended that the injections be carried out with the patient in the dorsorecumbent position.

Summary

Epicondylitis of the humerus, though commonplace, is often misdiagnosed and mistreated.

The causative factor of this condition is unknown.

The lateral epicondyle is more frequently involved, and it occurs in this study in 383 out of 391 cases.

This condition occurs predominantly in males (ratio 4:1).

The type of pain pathognomonic of this condition is produced over the site of the lesion when the elbow is extended and when the wrist is dorsiflexed against applied resistance.

The pathology of lateral epicondylitis is described, as well as radiohumeral bursitis, and radiohumeral synovitis—closely allied pathological conditions.

Local injections of chloroprocaine (Nesacaine) and prednisolone (Meticortelone) for epicondylitis failed in only 21 patients in this total series of 391 patients.

30 The Fenway (15)

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Editorial

The Intestinal Phase of Gastric Secretion

The intestinal phase of gastric secretion refers to the fact that gastric secretion is stimulated under certain circumstances by the introduction of food into the upper portions of the small intestine. This stimulation seems to be mediated by a humoral agent, since it is exhibited by the vagus-denervated total stomach pouch or the Heidenhain pouch. The most satisfactory demonstration of the intestinal phase of secretion is made using a vagus-denervated total stomach pouch. During fasting such a pouch secretes little or no acid but secretes moderate amounts of gastric juice in response to food taking. Under these conditions, food that has not been acidified by mixture with the gastric content is the stimulating agent. This fact is of great significance, since it is now well established that the introduction of acid solutions into the duodenum inhibits gastric secretion, probably by means of an inhibitory hormone released from the duodenal mucosa. In this connection it is of interest that preparations of pancreatic secretin prepared by the Lilly Company, when injected intravenously in dogs, cause a profuse secretion of pancreatic juice and a simultaneous inhibition of gastric secretion.[1]

Since food entering the duodenum has usually been acidified by mixture with gastric juice, it seems likely that the intestinal phase of gastric secretion is of little consequence in normal persons. This is suggested by the fact that gastric secretion from a vagus-denervated Heidenhain pouch is almost completely abolished by excision of the antrum.[2] In this experiment food acidified with gastric secretion from the main stomach passes directly into the duodenum with little, if any, stimulation of gastric secretion. It is probable, however, that shortly after meal taking some food escapes from the stomach into the duodenum. This is suggested by the occasional rapid passage of a liquid barium meal through the pylorus. Under these conditions, the food may not be sufficiently acid to stimulate release of the inhibitory hormone from the duodenum, but, on the other hand, may stimulate the release of a gastric secretory hormone similar to gastrin in function. It is also conceivable that the intestinal phase of secretion may be of significance in certain patients in whom the nervous phase of gastric secretion and the gastric phase are both inadequate to produce sufficient stimulation of gastric secretion to acidify the gastric content. It may well be that the intestinal phase of secretion represents an auxiliary gastric-secretory-stimulating mechanism which becomes effective only when the nervous phase and the gastrin phase are inadequate.

Both the antrum phase of secretion and the intestinal phase may become of real consequence in patients who have had the Finsterer-Devine exclusion type of partial gastrectomy. Under these conditions, the stump of stomach is anastomosed to the side of the first portion of the jejunum. Stoma ulcers are particularly frequent as a sequel to this operation. The cause of this high incidence of ulceration may well be the fact that food from the stomach regurgitates proximally through the duodenum and even through the pylorus into the excluded antrum. It is likely that during this regurgitation the food becomes neutralized by the secre-

tions of the duodenum. This neutral food is optimum for stimulating the intestinal phase of secretion and also for causing the release of gastrin from the excluded antrum. In both cases, stimulation proceeds uninterruptedly because the food does not become acidified as it does under normal conditions. These observations suggest that from the physiological point of view the Billroth I operation is superior to the Billroth II.

While the humoral agent responsible for the intestinal phase of gastric secretion may be gastrin, certain observations in the laboratory suggest that this is not the case. The stimulation could be due to secretagogues in the food. Evidence in favor of a specific hormone like gastrin could be secured if it could be demonstrated that distention within physiological limits of the upper part of the duodenum would produce a stimulation of secretion in the Heidenhain pouch, as it does when such a stimulus is applied to the antrum.

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Case Reports

Spontaneous Pneumoperitoneum

ARTHUR R. WRIGHT, M.D., Jamaica, N. Y.

Spontaneous pneumoperitoneum can be defined as air within the peritoneal cavity without an associated demonstrable lesion or evidence of peritonitis. One apparent etiologic factor in the female would be the spontaneous insufflation of air through the Fallopian tubes, and this has been reported.[1, 3,4,6,7] I should like to review the entire subject of pneumoperitoneum and present a case of spontaneous pneumoperitoneum occurring in this manner.

Pneumoperitoneum is usually incidental to intraperitoneal disease. Peptic ulcer perforation, rupture of a gangrenous appendix, and leakage from diverticulitis of the sigmoid colon would account for most cases of pneumoperitoneum, but rarer causes should be considered in a differential diagnosis. Pneumatosis cystoides intestinalis is a disease characterized by the presence of small blebs along the intestinal wall, caused most likely by the forcing of gas into lymphatic channels through minute mucosal ulcerations. Although a self-limited disease with rapid healing, these blebs may rupture, with the symptoms associated with pneumoperitoneum without peritonitis. Briggs, Sifra, and Overholt [8] report that this disease is being seen with increasing frequency, and many small series of cases have been reported. Pneumoperitoneum incidental to pulmonary emphysematous disease adjacent to the diaphragm with probable perforation into the peritoneal cavity is another possible cause.[2] Accidental pneumoperitoneum following douching has been the subject of reports,[1,3,4] and instances have made up many of the reported cases classified as spontaneous pneumoperitoneum. When pneumothorax was widely used in the treatment of tuberculosis, accidental pneumoperitoneum was not uncommon, and the accidental perforation of a viscus during endoscopy is usually confirmed by the presence of free subdiaphragmatic air. Purposeful pneumoperitoneum through tubal insufflation is used frequently in the Rubin's test for tubal patency, and infrequently in special diagnostic roentgen studies of the abdomen by introducing air by needle puncture through the abdominal wall.

Spontaneous pneumoperitoneum, with the passage of air from the vagina via a patulous cervix into the uterus and Fallopian tubes to the peritoneal cavity, is not uncommon in the postpartum state. Several reports of pneumoperitoneum following knee-chest postpartum exercises have appeared, with the recommendation that these exercises be discouraged.[4,5,7] Even fatal air embolism has been reported from this source when air entered a patent vein within the uterus.[9] Spontaneous pneumoperitoneum via the female genital tract not in the puerperal state is rare, and only one reported case has been found. Fredrikson [7] described a patient with recurrent attacks of pneumoperitoneum who had no abnormalities at operation and who was cured after bilateral salpingectomy. Her repeated episodes of pneumoperitoneum were not related to physical exercise, coitus, or menstruation. The case presented is another proved case of spontaneous pneumoperitoneum via tubal insufflation.

Submitted for publication Oct. 14, 1958.

From the Surgical Service, U. S. Army Hospital, Augsburg, Germany, APO 178, New York.

Report of a Case

A 25-year-old woman was first seen in the emergency room on March 12, 1958, complaining of severe epigastric and right shoulder pain. The onset of pain had occurred while she was bending over, tying her shoes, 24 hours prior to admission and at first had been limited to the left lower quadrant. The pain had been moderately severe, and the patient had stayed in bed at home before coming to the hospital.

The past history was significant in that she had been seen in the outpatient department on several occasions during the previous six-month period complaining of upper abdominal pain. A presumptive diagnosis of peptic ulcer disease had been made, and the patient was placed on a bland diet and antacids. An upper gastrointestinal x-ray study had been reported as negative in January, 1958. In 1953 an ovarian mass had been palpated on the right side, and a right oophorectomy had been done for cystic disease of the ovary. Her menarche had taken place at the age of 14, and she had always had premenstrual cramping. She was multiparous, with two full-term deliveries. Since her last delivery, in September, 1957, her periods had been irregular, and her last menstrual period was on March 1, 1958. Since the end of that period she had had a minimal pinkish vaginal discharge.

On physical examination, the abdomen was tense in the upper quadrants, and the bowel sounds were present but hypoactive. Maximum tenderness was elicited in the epigastrium, but tenderness was also present in the left lower quadrant. The white cell count was 7,500 per cubic millimeter and the temperature 99 F. An upright x-ray of the abdomen revealed a large amount of air under both leaves of the diaphragm (Fig. 1). Because of the evidence of free air and the history suggestive of duodenal ulcer, a diagnosis of ruptured ulcer was made and the patient prepared for laparotomy. At operation, there was minimal free peritoneal fluid but no evidence of peritoneal irritation. The gastrointestinal tract was examined from cardia to upper rectum without abnormal findings. At this point the possibility of tubal insufflation was first considered and the Fallopian tubes examined. The right tube was bound down by adhesions from the previous operation, but the left tube was free and slightly injected. A blunt 15-gauge needle was introduced into the fimbriated end, and air from a syringe could be easily passed into the uterus by allowing the weight of the syringe barrel to fall by gravity. The diagnosis of spontaneous pneumoperitoneum through tubal insufflation was made and the abdomen closed.

Postoperatively the patient stated she often expelled gas from her vagina on bending over and recalled that this had occurred on the morning of her onset of symptoms. The postoperative course was uneventful, and the patient was taught how to tighten her perineal muscles when stooping or bending. She was next seen in the emergency room on April 11, with epigastric pain, and a flat plate of the abdomen was taken (Fig. 2). Her pain subsided after 48 hours of bed rest and sedation. Before leaving the hospital, she was fitted with a cervical diaphragm and instructed to wear it at all times when out of bed. She was next seen three months later with similar complaints, and again had demonstrable subdiaphragmatic air. She stated that the diaphragm was uncomfortable and that she had stopped using it one week previously. Another diaphragm was fitted, and she was sent home. She was last seen in September, 1958, without symptoms, but she stated that she had experienced epigastric pain at the time of each of her last two periods, during which time her diaphragm was out. The possibility of tubal ligation if the symptoms continued was discussed with the patient.

Comment

The case demonstrates why spontaneous pneumoperitoneum by insufflation of the genital tract must be considered if unneces-

Figure 1

Figure 2

sary laparotomy is to be avoided. Even though the onset of pain occurred 24 hours before this patient sought medical help, she appeared acutely ill, and it was felt by the examiner that a small perforation had occurred at the onset of pain, which temporarily became sealed and then reopened after the patient had breakfast the following day. In retrospect, the temperature and blood picture did not support the diagnosis of peritonitis. If the possibility of pneumoperitoneum by genital-tract insufflation had been considered, and the patient questioned about the escape of air from her vagina, the unnecessary surgery could have been avoided. Although not frequently reported, spontaneous pneumoperitoneum occurs often enough to be considered in the differential diagnosis of every woman demonstrating subdiaphragmatic air by x-ray.

Summary

Pneumoperitoneum is classified according to etiology, and the various causes are discussed.

A case of proved pneumoperitoneum by spontaneous insufflation through the genital tract is presented, and the avoidance of unnecessary surgery is discussed.

It is suggested that spontaneous pneumoperitoneum by insufflation through the Fallopian tubes is not as infrequent as has been reported, and this etiology should be considered in the differential diagnosis of every female patient with pneumoperitoneum.

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Excision of Obstructing Retropharyngeal Tumor in an Infant

Excision by Sagittal Jaw-Splitting Approach

SAMUEL L. PERZIK, M.D.; HENRY J. RUBIN, M.D., Beverly Hills, Calif., and RICHARD SCHORR, M.D., Los Angeles

The choice of a surgical approach to the pharynx depends upon the location and size of the lesion under consideration. If primarily located in the oropharynx, a direct transoral approach is usually adequate. The nasopharynx may also be reached through an intraoral approach with or without a soft-palate-splitting incision or removal of part of the posterior bony palate.[1] If this is not adequate, a lateral pharyngotomy with or without a transection at about the angle of the mandible [2] may yield a good exposure of the nasopharynx. In certain instances a transantral approach through a Caldwell-Luc or Weber-Fergusson incision may be elected. The hypopharynx may be reached by suspension laryngoscopy or through an anterior [3] or lateral pharyngotomy exposure. Very extensive lesions in these areas, especially those that require complete extirpation with a maximum of safety, challenge the effectiveness of any of these surgical approaches. A situation of this type in an adult was managed by Klopp [4] through a sagittal transection of the lower jaw. In the procedure he split the lower lip, chin, mandible, submental triangle, and tongue back to the vallecula. When faced with a similar retropharyngeal tumor problem in a 3-month-old infant, this approach was utilized with complete satisfaction.

Report of Case

A 2-month-old Negro girl was admitted to the pediatric service of the Cedars of Lebanon Hospital on May 29, 1958, with increasing dyspnea, dysphagia, and weight loss, with onset at the age of 3 weeks. After being treated elsewhere for a "cold" and "laryngotracheal malacia," she was admitted here with a diagnosis of possible retropharyngeal tumor.

On entrance there was stertorous breathing, with sternal retraction and distended neck veins; respiratory rate was 30 per minute. There was inspiratory and expiratory stridor, with flaring of the alae nasi. Dysphagia with regurgitation and immediate oral accumulation of food and mucus were present at feeding. She took less than 1 oz. (30 cc.) of formula every two hours and weighed 7 lb. 12 oz. (3,515 gm.). The pulse was 160 a minute and regular.

The roentgenogram revealed a soft-tissue density of the retropharynx with forward displacement of the airway. The hemogram revealed a hemoglobin of 15.1 gm/100 cc. and a hematocrit of 45 vol. %.

On May 30, a No. 00 cannula was inserted through a low tracheostomy, performed under local anesthesia. On the next day, with the patient under ether anesthesia, the presence of a large firm sessile retropharyngeal tumor was verified. It extended from the nasopharyngeal vault down to the lowest level of the hypopharynx. It was dome-shaped, nonulcerated, and firmly wedged between the lateral pharyngeal walls (Fig. 1). It could be outlined with the finger but not entirely visualized because of its extent. A biopsy specimen taken from the oropharyngeal surface of the tumor was not diagnostic.

Because of the poor physical status of the child, a period of gavage feeding was attempted. By July 12, the child weighed 9 lb. 2 oz. (4,139 gm.), but dysphagia had increased to such a degree that continued feeding was becoming almost impossible, apparently owing to the increased growth of the tumor.

On July 15, under ether-oxygen anesthesia, with the endotracheal tube passed through the No. 00 metal cannula, definitive surgery was instituted. The fixed sessile retropharyngeal mass extended

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From the Departments of Pediatrics and Surgery, Cedars of Lebanon Hospital.

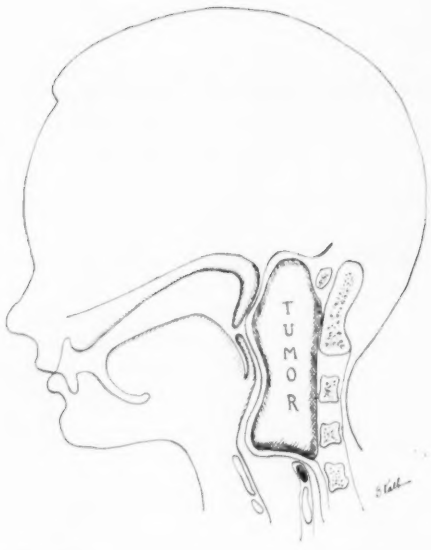
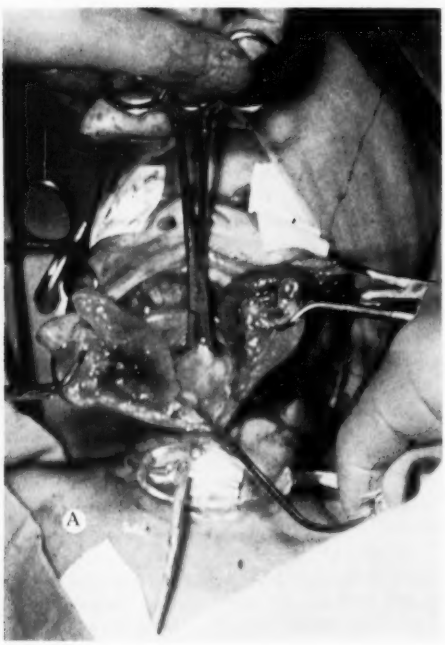
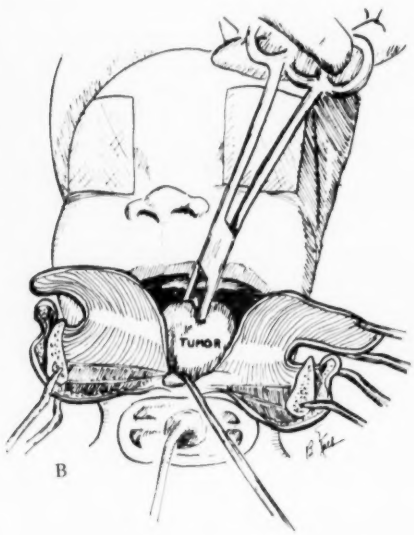


Fig. 1.—The tumor in the retropharyngeal space extends from the roof of the nasopharynx to the floor of the hypopharynx. It pushes the soft palate, tongue, and epiglottis forward, thus blocking the laryngeal vault and the esophageal orifice.

from the nasopharyngeal vault down to the cricopharynx and was incarcerated between the outward bulging lateral pharyngeal walls. The soft palate, tongue, and epiglottis were pushed far forward by the tumor. In situ it measured about 7 cm. in each diameter. It was decided that removal of this mass by a conventional approach would not be possible. Therefore, intraoral removal with splitting of the soft palate, or lateral or anterior pharyngotomy, or any combination of these avenues, was rejected. A procedure first described by Dr. Calvin Klopp was therefore chosen.[4] This consisted of a front-to-back midline transection of the lower jaw from the lip to the vallecula. The lower lip and chin were incised in the midline down to the hyoid bone. The mandible was then transected in the anterior midline, and the anterior floor of the mouth and tongue, and the submental triangle musculature, were all incised in the midline all the way back to the lingual base of the epiglottis in the vallecula. The lower jaw and the lower half of the oral cavity were thus separated into two parts, which were spread widely in the lateral plane, visually revealing the full extent of the retropharyngeal tumor (Fig. 2*A* and *B*). The tumor was nonulcerated and firmly bound by fibrous strands to the anterior surfaces of the vertebral bodies. It was otherwise encapsu-

Fig. 2.—(*A*) After sagittal section of the lower jaw (lip, chin, submental triangle, mandible, floor of the mouth, tongue, and vallecula) the tumor is pulled forward with a towel clip. The epiglottis is retracted downward by a tenaculum. (*B*) Diagrammatic representation of *A*.





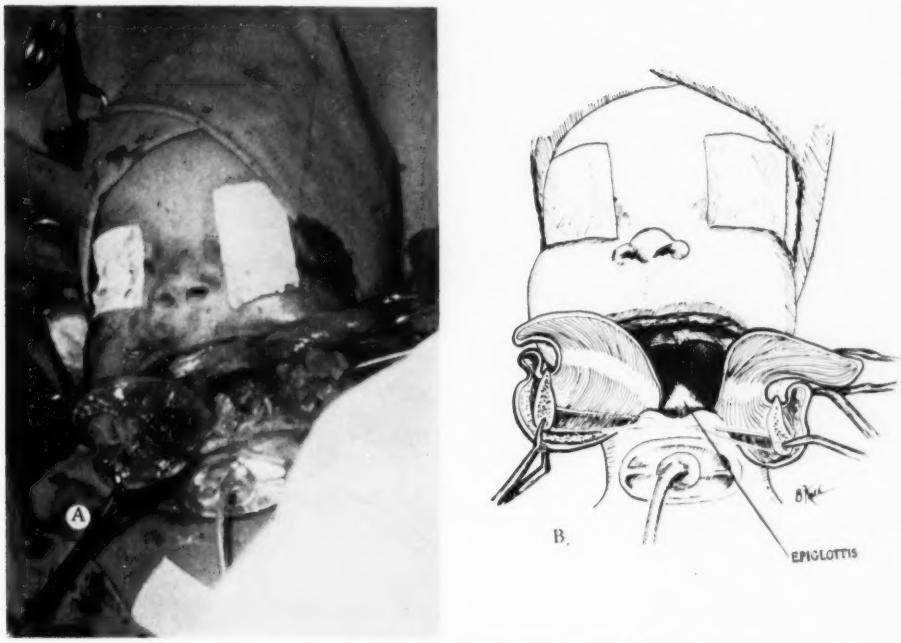


Fig. 3.—(*A*) After removal of tumor, the empty oropharynx is seen between the replaced soft palate and the epiglottis. (*B*) Diagrammatic representation of *A*.

lated and deep to the superior constrictor muscle. The latter, with the overlying mucosa, was split in the vertical midline and peeled off the tumor. Only by sharp dissection was it possible to free the tumor from its marked adherence to the prevertebral surface (Fig. 3*A* and *B*). The pharyngeal mucosa, vallecula, tongue, floor of the mouth, inferior gingiva, submental muscles (geniohyoid and mylohyoid), lower lip, and chin were closed with interrupted sutures after approximating the cut ends of the mandible with stainless steel wire. A Penrose drain was inserted, but no support for the mandible was used. A No. 8 polyvinyl infant feeding tube was passed through the nostril into the stomach. The No. 00 tracheostomy tube was left in position.

The postoperative course was quite stormy during the first four hours because of two rather vigorous hemorrhages from the mouth, which were controlled by packing. Blood 50 cc. was given during the two and a half hours of surgery and 100 cc. during the first postoperative day. During the first six postoperative days the rectal temperature fluctuated between 101 and 97 F. Antibiotics were discontinued on the second postoperative day. Clinically the mandible appeared to be firm on the 12th postoperative day, at which time oral feeding was begun. The child showed a little difficulty in grasping the nipple with the lips, but

Fig. 4.—Photograph three months after operation, revealing the excellent restoration of jaw contour and mucocutaneous lower lip alignment.

for only 24 hours. Because of the formation of an intratracheal and subglottic granuloma, decannulization was not accomplished until the 28th postoperative day, at which time the child weighed 10 lb. 6½ oz. (4,720 gm.) and reacted normally in all respects. Functionally and cosmetically the recovery was well within normal limits. The contour of the lower jaw and the mucocutaneous junction of the lower lip were excellent, and the midline scar was inconspicuous (Fig. 4).

The specimen consisted of a 5×3.5×2.5 cm. smooth, glistening mass which revealed white fibrous tissue on section. Microscopically it revealed largely fibrillar connective tissue with fascicles suggesting neurogenic tumor. In places structures resembling nerve bundles had formed. The tumor also contained a number of lobules of adipose tissue, some of which were immature. It was diagnosed as a neurofibrolipomatous hamartoma.

Summary

A radical approach to the entire pharynx for removal of a large obstructing hamartoma in an infant is described. The Klopp sagittal section of the lower jaw and oral content was successfully utilized in this case.

300 South Beverly Dr. (Dr. Perzik).

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CORRECTION

In the January issue of the ARCHIVES, the title of the article by Dr. Elmer Hoffman was incomplete both on the cover and on page 177. It should read as it appears in the Table of Contents—Acute Pancreatitis Due to a Peri-Vaterine Duodenal Diverticulum.

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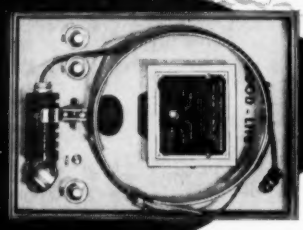

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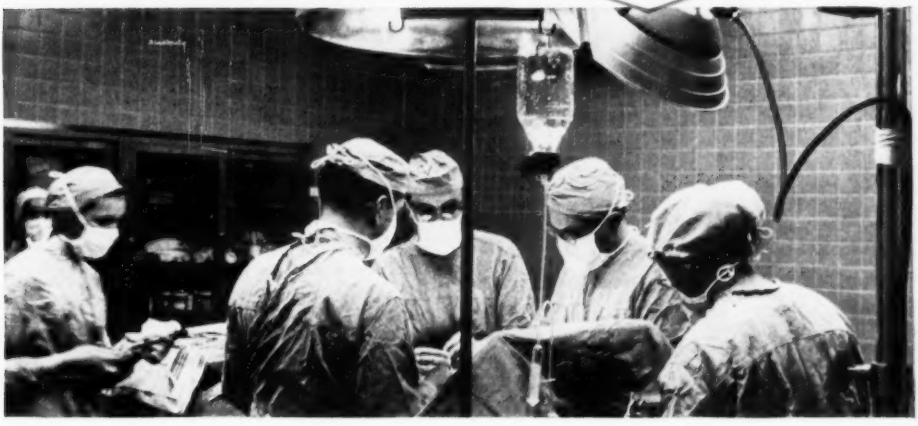

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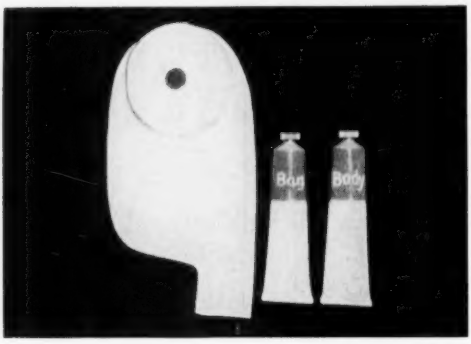

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by Oren C. Durham, 2 pages, 5 cents

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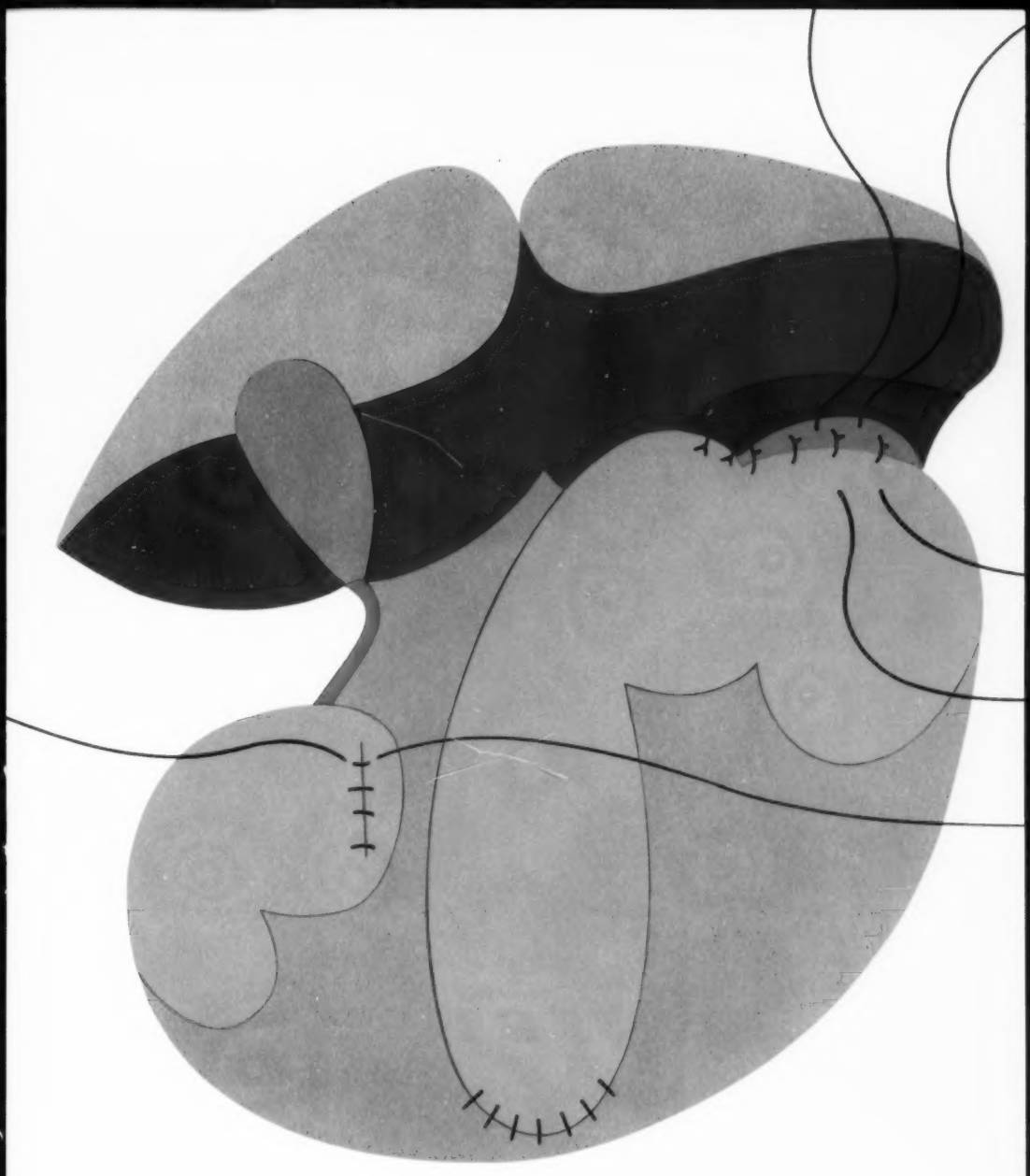

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Oatmeal is an outstanding source of natural nutrients well suited for debilitated patients. It ranks highest among whole-grain cereals in content of protein, thiamine, and phosphorus.

The oatmeal serving with milk provides high-quality protein, unimpaired in processing or preparation. It supplies the essential amino acids in proper proportions for biosynthesis, repair, and replenishment of tissue. Oatmeal also provides significant amounts of several B vitamins and minerals important to physiologic rehabilitation.

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Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

IN POSTSURGICAL NUTRITION oatmeal finds a well-merited place as soon as feedings no longer need be limited to clear liquids. Its high nutrient value and blandness aid in rapid, uneventful re-alimentation.

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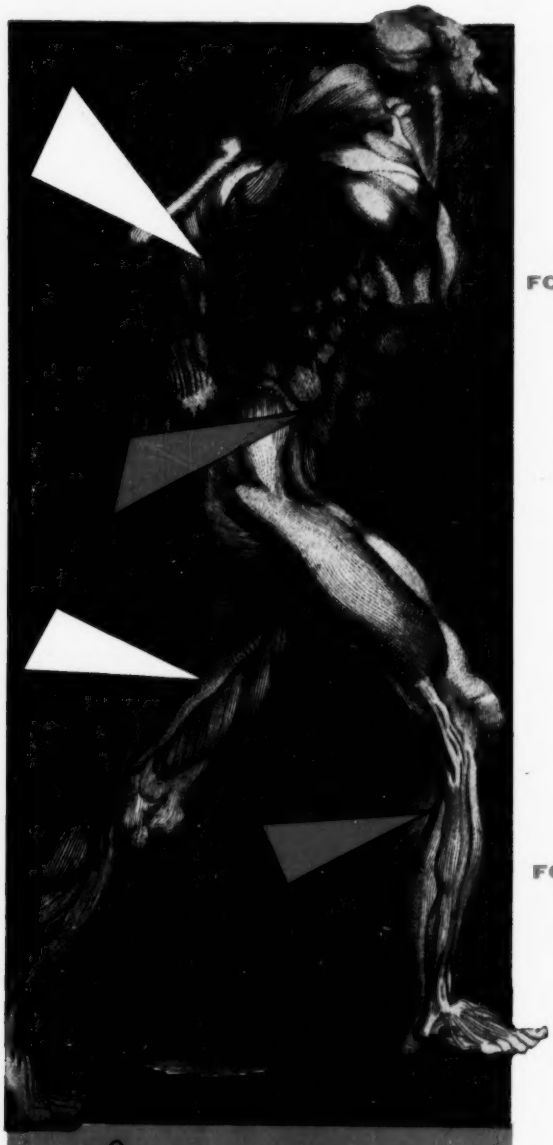

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5% solution (50 mg. per cc.)
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Ampuls of 1 cc.
Ampuls of 1.5 cc.
Ampuls of 2 cc.
Vials of 30 cc.

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Ampuls of 1 cc.
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Disposable syringes of 1 cc.

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Powder, vials of 15 Gm.

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